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Exercise and Falls among Frail Older People — Special Focus on People with Dementia

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EXERCISE AND FALLS AMONG FRAIL OLDER PEOPLE – SPECIAL FOCUS ON PEOPLE WITH DEMENTIA

Niko M. Perttilä

ACADEMIC DISSERTATION

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Exercise may be the best medicine.

CONTENTS

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II. Perttila NM, Öhman H, Strandberg TE, Kautiainen H, Raivio M, Laakkonen ML, Savikko N, Tilvis RS, Pitkala KH: Severity of frailty and the outcome of exercise intervention among participants with Alzheimer disease: A sub-group analysis of a randomized controlled trial. European Geriatric Medicine 2016;7:117-121.

III. Perttila NM, Ohman H, Strandberg TE, Kautiainen H, Raivio M, Laakkonen ML, Savikko N, Tilvis RS, Pitkala KH: How do community-dwelling persons with Alzheimer disease fall? Falls in the FINALEX study. Dement Geriatr Cogn Dis Extra 2017;7:195-203.

IV. Perttila NM, Ohman H, Strandberg TE, Kautiainen H, Raivio M, Laakkonen ML, Savikko N, Tilvis RS, Pitkala KH. Effect of Exercise on Drug-Related Falls Among Persons with Alzheimer's Disease: A Secondary Analysis of the FINALEX Study. Drugs Aging 2018; https://doi.org/10.1007/s40266-018-0594-7

The publications are referred to in the text by their roman numerals. The papers are reprinted with the permission of the copyright holders. In addition, some unpublished material is presented.

ABBREVIATIONS

AD	Alzheimer Disease
ADL	Activities of daily living
AFC	Advanced Frailty Control (group)
AFI	Advanced Frailty Intervention (group)
ATC	Anatomic Therapeutic Chemical (classification)
BMI	Body Mass Index
CDR	Clinical Dementia Rating
CG	Control Group
CHD	Coronary Heart Disease
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CVD	Cardiovascular Disease
DAP	Drug with Anticholinergic Properties
DLB	Dementia with Lewy bodies
DM	Diabetes Mellitus
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, IVth edition
EFS	Edmonton Frail Scale
EN	Exercise and Nutrition
EP	Exercise and Placebo (nutrition)
FI	Frailty Index
FIM	Functional Independence Measure
FIMmotor	Motor part of the Functional Independence Measure
FINALEX	Finnish Alzheimer disease exercise trial
FRD	Fall-Related Drug
GE	Group Exercise
HBS	Helsinki Businessmen Study (measure)
HE	Home Exercise
HRQoL	Health-Related Quality of Life
IG	Intervention Group
IGF-1	Insulin-like Growth Factor 1
IL-6	Interleukin 6
IQR	Interquartile range
IRR	Incidence Rate Ratio
IU	International Unit
MFGM	Milk Fat Globule Membrane
MMSE	Mini-Mental State Examination
MNA	Mini-Nutritional Assessment

NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association
NNT	Number Needed to Treat
OR	Odds Ratio
PDD	Parkinson's Disease with Dementia
PPT	Physical Performance Test
PRC	Prefrail Control (group)
PRI	Prefrail Intervention (group)
PST	Problem-Solving Therapy
PYRS	Person-years
QoL	Quality of Life
RCT	Randomized Controlled Trial
SD	Standard Deviation
SPPB	Short Physical Performance Battery
VAD	Vascular Dementia
WHI-OS	Women's Health Initiative Observational Study
WHO	World Health Organization
95% CI	95% Confidence Interval

ABSTRACT

Background: The term frailty is used to describe older persons who are at increased risk of adverse health outcomes. Various measures have been investigated but Fried's criteria are used most often. However, there is still a lack of consensus on the definition of frailty. Simpler measures based on postal questionnaires have also been investigated in the assessment of frailty. Different measures may only partly identify the same persons as frail, and in addition the predicted outcomes may vary depending on the measure used.

Older persons in general and older frail persons have benefited from exercise interventions. Some studies have also revealed that persons with dementia may benefit from exercise intervention. However, there is a lack of evidence on whether or not the stage of frailty affects the outcomes of exercise intervention among persons with dementia.

Among older persons in general, known risk factors of falls are, for example, a history of falls, muscle weakness, gait deficit, arthritis, depression, polypharmacy, psychotropic medication and older age. Fewer studies have concerned risk factors of falls among persons with dementia. No study has been carried out to investigate possible interactions between exercise, fall-related drugs and falls among people with dementia.

Aims: This study aimed to investigate how various frailty measures overlap, whether or not they identify the same persons as frail, and to explore if the outcomes are similar irrespective of the used measure. This study also investigated whether or not the frailty status of community-dwelling persons with Alzheimer Disease (AD) affects the outcomes of exercise intervention. In addition, this study explored risk and protective factors associated with falls among persons with AD and whether there are interactions between exercise intervention, fall-related drugs, and falls in this population.

Subjects and methods: The subjects in Study I were the participants of the Helsinki Businessmen Study, which is a long-term observational study of men born in 1919–1934. These men were investigated by analyzing their responses in postal questionnaires in 2000 and 2005. A total of 480 men were included in the study, and their mean age was 73 years at the start of follow-up. Two phenotype-based measures, the Helsinki Businessmen Study (HBS) measure and the modified Women's Health Initiative Observational Study (WHI-OS) measure, and the Frailty Index (FI), consisting of 20 items, were used to identify frailty through postal questionnaires. The measures were investigated in regard to how they overlapped in identifying robust, prefrail and frail individuals and how they predicted falls, health-related quality of life (HRQoL, 15D instrument), weight change and mortality during a five year follow-up period.

The subjects in Studies II, III and IV were the participants of the Finnish Alzheimer disease exercise trial (FINALEX), which was an exercise

intervention study among home-dwelling persons with AD. The mean age of the participants (N=194) was 78 years and 39% were women. The participants in intervention groups underwent group-based or home-based exercise for one hour twice weekly for 12 months (N=129), and the control group had normal care (N=65). In the FINALEX study, falls were recorded in fall diaries by AD persons' spousal caregivers during the one-year follow-up period. In Study II, both the combined intervention group and the control group were subdivided into prefrail (0–1 criteria) and advanced frailty (2–5 criteria) according to modified Fried phenotypic criteria. The number of falls per person-years and changes in the Functional Independence Measure (FIM) served as outcome measures.

In Study III, all participants were investigated together to reveal fall risk factors in connection with physical functioning, diseases and drugs. Study IV investigated possible interactions between exercise and fall-related drugs by comparing the incidence rate ratios (IRRs) of falls among non-users and users of various drugs in intervention and control groups.

Results: Both the HBS measure and the WHI-OS measure identified 7.3% of the participants of the Helsinki Businessmen Study as frail, but only partly were they the same individuals. The FI measure identified 17.9% of the participants as frail. Altogether, 21.3% of the participants were classified as frail by at least one measure. All measures (HBS, WHI-OS, FI) predicted a significantly higher number of fallers, lower HRQoL, and higher mortality among frail participants than among prefrail and not frail participants. There were no differences as regards weight changes between the frailty stages or frailty groups.

In the FINALEX study, in the prefrail groups the average rate of falls was significantly lower in the intervention group than in the control group (1.14 falls/person per year [95% confidence interval (CI): 0.90 to 1.43] and 1.82 falls/person per year [95% CI: 1.40 to 2.32], respectively; IRR 0.63 [95% CI: 0.45 to 0.89]; P=0.008 adjusted for sex, age and comorbidities). In the advanced frailty groups also, the participants in the intervention group had a significantly lower rate of falls than those in the control group (2.15 falls/person per year [95% CI: 1.76 to 2.59] and 5.32 falls/person per year [95% CI: 4.36 to 6.44], respectively; IRR 0.43 [95% CI: 0.33 to 0.57]; P<0.001 adjusted for sex, age and comorbidities). Both intervention groups also deteriorated significantly more slowly than their respective control groups according to changes in FIM scores.

Better physical functioning and robustness protects against falls among persons with AD. Diseases such as chronic obstructive pulmonary disease, diabetes and arthritis, as well as drugs such as opioids, psychotropics, drugs with anticholinergic properties, and polypharmacy were associated with an increased risk of falls. Use of antihypertensives was associated with a reduced risk of falls among those undertaking exercise, but there was an increased risk of falls in the control group. Exercise also reduced fall risk among users of psychotropics.

Conclusions: The HBS measure, the WHI-OS measure and the FI measure identified frail participants, but there was only a partial overlap. The FI identified more persons as frail. All three measures predicted increased falls and mortality and reduced HRQoL among the frail participants.

People with AD may benefit from exercise intervention irrespective of their frailty status in respect of falls and physical functioning. Better physical functioning and robustness protect against falls. Several diseases and drugs were risk factors of falls. Exercise favorably interacted with antihypertensives and psychotropics as regards the risk of falls.

TIIVISTELMÄ

Tutkimuksen tausta: Termiä gerastenia käytetään kuvaamaan hauraita ikääntyneitä ihmisiä, joilla on suurentunut riski haitallisille päätetapahtumille. Erilaisia mittareita on tutkittu, mutta useimmiten on käytetty Friedin kriteerejä. Kuitenkaan yhteisymmärrystä gerastenian määritelmästä ei ole vielä saatu aikaan. Myös yksinkertaisempia kyselyihin perustuvia mittareita on tutkittu gerastenian arvioimiseksi. Eri mittarit saattavat tunnistaa gerastenisiksi vain osittain samoja henkilöitä, ja myös ennustetut päätetapahtumat saattavat vaihdella käytetystä mittarista riippuen.

Iäkkäät ihmiset yleensä ja gerasteniset iäkkäät ihmiset ovat hyötyneet useissa tutkimuksissa liikuntainterventiosta. Muutamissa tutkimuksissa on nähty, että myös ihmiset, joilla on muistisairaus, voivat hyötyä liikuntainterventiosta. Kuitenkaan ei ole näyttöä, vaikuttaako gerastenian aste liikuntainterventiosta hyötymiseen muistisairailla henkilöillä.

Tiedettyjä ikääntyneiden ihmisten yleisiä riskitekijöitä kaatumisille ovat esimerkiksi kaatumishistoria, lihasheikkous, kävelyvaikeus, nivelrikko, masennus, monilääkitys, psyykelääkkeiden käyttö ja korkeampi ikä. Selvästi vähemmän on tutkimuksia kaatumisten riskitekijöistä muistisairailla henkilöillä. Aikaisempia tutkimuksia mahdollisista interaktioista liikunnan ja kaatumisiin liittyvien lääkkeiden välillä suhteessa kaatumisiin ei ole muistisairailla potilailla.

Tutkimuksen tavoitteet: Tämä tutkimus tutki, kuinka eri gerastenian mittarit limittyvät toistensa suhteen, tunnistavatko ne samoja henkilöitä gerastenisiksi ja ovatko päätetapahtumat samanlaisia riippumatta käytetystä mittarista.

Tämä tutkimus myös tutki, vaikuttiko gerastenian aste liikuntainterventiosta hyötymiseen kotona asuvilla Alzheimerin tautia sairastavilla henkilöillä.

Lisäksi tämä tutkimus selvitti kaatumisiin liittyviä suojaavia ja riskiä lisääviä tekijöitä Alzheimerin tautia sairastavilla henkilöillä, ja onko liikuntainterventiolla ja kaatumisiin liittyvillä lääkkeillä interaktioita kaatumisten suhteen tässä joukossa.

Aineisto ja menetelmät: Osatutkimuksen I aineistona ovat osallistujat Helsinki Johtajat –tutkimuksessa, joka on pitkäaikainen havaintotutkimus vuosina 1919-1934 syntyneistä miehistä. Näitä miehiä tutkittiin heidän vuosina 2000 ja 2005 postitse antamiensa kyselyvastaustensa perusteella. Yhteensä 480 miestä sisältyi tutkimukseen ja heidän keski-ikänsä oli 73 vuotta seurannan alussa. Kaksi ilmiasuun perustuvaa mittaria, Helsinki Johtajat –tutkimuksen mittari HBS (eng. Helsinki Businessmen Study) ja muokattu Women's Health Initiative Observational Study (WHI-OS), sekä gerastenian indeksimittari (eng. Frailty Index, FI), joka koostui 20 kohdasta, rakennettiin

tunnistamaan gerasteniaa kirjekyselyn perusteella. Mittareita tutkittiin, kuinka ne menivät päällekkäin ei-gerastenisten, esi-gerastenisten ja gerastenisten henkilöiden tunnistamisessa ja kuinka ne ennustivat kaatumisia, terveyteen liittyvää elämänlaatua, painonmuutosta ja kuolleisuutta viiden vuoden seurannassa.

Osatutkimuksien II, III ja IV aineistona ovat osallistujat FINALEX-tutkimuksessa, joka oli liikuntainterventiotutkimus kotona asuvilla Alzheimerin tautia sairastavilla henkilöillä (eng. Finnish Alzheimer disease exercise trial). Osallistujien (yhteensä 194 henkilöä) keski-ikä oli 78 vuotta ja 39 % heistä oli naisia. Osallistujat liikuntainterventioryhmissä (yhteensä 129 henkilöä) saivat joko ryhmäliikuntainterventiota tai kotiliikuntainterventiota yhden tunnin kerrallaan kahdesti viikossa 12 kuukauden ajan, ja kontrolliryhmä (yhteensä 65 henkilöä) sai normaalia kunnallista hoitoa. FINALEX-tutkimuksessa Alzheimerin tautia sairastavien osallistujien puolisot seurasivat kaatumisia kaatumispäiväkirjojen avulla 12 kuukauden seurannan ajan. Osatutkimuksessa II sekä yhdistettu liikuntainterventioryhmä että kontrolliryhmä jaettiin esi-gerastenisiin (0-1 kriteeriä) ja enemmän gerastenisiin (2-5 kriteeriä) muokattujen Friedin kriteerien mukaisesti. Kaatumiset henkilövuotta kohden ja muutokset FIM-toimintakykymittarissa (Functional Independence Measure) toimivat tulosmuuttujina.

Osatutkimuksessa III kaikkia osallistujia tutkittiin yhdessä kaatumisiin liittyvien riskitekijöiden, kuten fyysisen toimintakyvyn, sairauksien ja käytettyjen lääkkeiden, suhteen. Osatutkimuksessa IV tutkittiin mahdollisia interaktioita liikuntaintervention ja kaatumisiin liittyvien lääkkeiden välillä vertaamalla kaatumisten ilmaantuvuustiheyksien suhteita (eng. incidence rate ratio, IRR) eri lääkkeiden käyttäjien ja ei-käyttäjien kesken liikuntainterventioryhmässä ja kontrolliryhmässä.

Tulokset: Sekä HBS-mittari että WHI-OS-mittari tunnistivat 7,3 % Helsinki Johtajat –tutkimuksen osallistujista gerastenisiksi, mutta näistä vain osa oli samoja henkilöitä. FI mittari tunnisti 17,9 % gerastenisiksi. Kaikenkaikkiaan 21,3 % osallistujista tunnistettiin gerastenisiksi vähintään yhden mittarin mukaan. Kaikki mittarit (HBS, WHI-OS, FI) ennustivat merkitsevästi enemmän kaatujia, huonompaa elämänlaatua ja suurempaa kuolleisuutta gerastenisille, kuin esi-gerastenisille tai ei-gerastenisille henkilöille. Painon muutoksen suhteen ei ollut eroja eri gerastenian asteiden tai mittareiden välillä.

FINALEX-tutkimuksessa esi-gerastenisissa ryhmissä keskimääräinen kaatumisten määrä oli merkitsevästi pienempi liikuntainterventioryhmässä kuin kontrolliryhmässä (1,14 kaatumista henkilövuotta kohden [95 %:n luottamusväli (eng. 95 % confidence interval, CI): 0,90-1,43] ja 1,82 kaatumista henkilövuotta kohden [95 % CI: 1,40-2,32]; IRR 0,63 [95 % CI: 0,45-0,89]; P=0,008 sukupuoli, ikä ja liitännäissairaudet huomioitu). Myös enemmän gerastenisissa ryhmissä keskimääräinen kaatumisten määrä oli merkitsevästi pienempi liikuntainterventioryhmässä kuin kontrolliryhmässä

(2,15 kaatumista henkilövuotta kohden [95 % CI: 1,76-2,59] ja 5,32 kaatumista henkilövuotta kohden [95 % CI: 4,36-6,44]; IRR 0,43 [95 % CI: 0,33-0,57]; P<0,001 sukupuoli, ikä ja liitännäissairaudet huomioitu). Kummankin liikuntainterventioryhmän fyysinen toimintakyky myös heikkeni merkitsevästi hitaammin kuin heidän vastaavien kontrolliryhmiensä FIM-toimintakykymittarin muutoksien perusteella.

Parempi fyysinen toimintakyky ja ei-gerastenisuus suojaavat kaatumisilta Alzheimerin tautia sairastavilla potilailla. Sairaudet, kuten keuhkoahtaumatauti, diabetes ja nivelrikko, sekä lääkkeet, kuten opioidit, psyykelääkkeet, lääkkeet, joilla on antikolinergisia ominaisuuksia, ja monilääkitys, liittyivät kohenneeseen kaatumisriskiin. Verenpainelääkkeiden käyttö liittyi alentuneeseen kaatumisriskiin liikuntainterventiota saaneilla, mutta kohonneeseen kaatumisriskiin kontrolliryhmällä. Liikuntainterventio vähensi kaatumisriskiä myös psyykelääkkeiden käyttäjillä.

Johtopäätökset: HBS-mittari, WHI-OS-mittari ja FI-mittari tunnistivat vain osittain samat henkilöt gerastenisiksi. FI tunnisti gerastenisiksi enemmän kuin muut. Kaikki kolme mittaria ennustivat suurempaa kaatumismäärää ja kuolleisuutta sekä huonompaa terveyteen liittyvää elämänlaatua gerastenisille osallistujille.

Alzheimerin tautia sairastavat henkilöt voivat hyötyä liikuntainterventiosta suhteessa kaatumisiin ja fyysiseen toimintakykyyn riippumatta gerastenian asteesta. Parempi fyysinen toimintakyky ja ei-gerastenisuus suojaavat kaatumisilta. Tietyt sairaudet ja lääkkeet olivat kaatumisten riskitekijöitä. Liikuntainterventiolla oli suosiollinen interaktio verenpainelääkkeiden ja psyykelääkkeiden kanssa suhteessa kaatumisriskiin.

1 INTRODUCTION

The term frailty is used to describe older persons whose health status has deteriorated without being a direct consequence of disease (Fulop et al. 2010). Frail persons often have disabilities (Fulop et al. 2010) and they are prone to various complications (Rockwood & Mitnitski 2007, Fulop et al. 2010). Although frail persons have existed throughout history the term frailty is relatively new (Strandberg et al. 2011). It was first used in the 1970s (Abellan van Kan et al. 2008a) and the definition is still developing (Strandberg et al. 2011). There is still no consensus of opinion as regards the official definition of frailty today (Fulop et al. 2010, Azzopardi et al. 2016).

Frailty is not a synonym for disability nor for comorbidity (Fried et al. 2004, Clegg et al. 2013). Nowadays the definition of frailty does not include the deterioration of functionality and a person does not have to have any disease to be frail (Fulop et al. 2010). However, often these are present at the same time (Rockwood et al. 2004). Frailty has a poor prognosis (Rockwood & Mitnitski 2007). It leads to disabilities, complications and an increased risk of mortality (Rockwood et al. 1994, Fried et al. 2001, Bortz 2002, Fried et al. 2004, Morley et al. 2006, Rockwood & Mitnitski 2007, Rolland et al. 2008, Fulop et al. 2010). Prevention and treatment of frailty have been intensively investigated in recent years (Clegg et al. 2013). So far the strongest evidence as regards preventing and treating frailty is for exercise (Strandberg et al. 2011).

The global prevalence of dementia is approximately 5–7%, Alzheimer disease (AD) being one of the most common types (Prince et al. 2013). It was estimated that 35.6 million people had dementia in 2010 and the number is expected to almost double every 20 years (Prince et al. 2013). Dementia and cognitive impairment are major risk factors of falls, as approximately 60% of persons with these conditions fall annually (Tinetti et al. 1988, van Dijk et al. 1993). Dementia and cognitive impairment also affect overall physical functioning, as they increase the risk of frailty, and vice versa (Robertson et al. 2013). The prevalence rates of both dementia and frailty increase with age, they are especially common among women, they have mutual etiological factors such as smoking, obesity, a low level of physical activity, and depression, and both of them also have poor prognosis as regards institutionalization and mortality (Sampson 2012). It has been suggested that cognition and frailty affect each other and also general health status with aging (Robertson et al. 2013). The prevalence of dementia has been found to be higher among frail persons than among robust people (Han et al. 2014, Kulmala et al. 2014).

A meta-analysis showed that physical exercise training may reduce the number of falls among persons with dementia or cognitive impairment (Chan et al. 2015). However, only a few exercise studies have concerned community-

dwelling persons with dementia (Pitkala et al. 2010). So far the most promising form of intervention seems to be intensive, long-term and diverse exercise training (Pitkala et al. 2010). Community-dwelling persons with AD have benefitted from intense and long-term exercise training in respect of physical functioning and falls without increasing the total cost of health and social services (Pitkala et al. 2013).

Exercise has been shown to be an effective way to prevent falls among cognitively intact people in several studies. However, there are only a few trials concerning the effects of exercise in dementia. Furthermore, although people with dementia are known to be prone to falls, little is known about why and how they fall and how their frailty and cognitive status interact with falls.

The present studies were carried out to investigate how various frailty measures identify older persons' frailty stages and how they predict health outcomes such as falls, quality of life (QoL) and mortality, and whether the stage of frailty has an effect on the benefits of exercise intervention among people with AD. These studies also concern the circumstances and associated factors of falls and whether there are interactions between exercise intervention and fall-related drugs (FRDs).

2 REVIEW OF THE LITERATURE

2.1 FRAILTY

The term frailty was first mentioned in the literature in the 1970s when it was used as a synonym for institutionalization (Abellan van Kan et al. 2008a). In the 1980s it was used to describe disabilities (Abellan van Kan et al. 2008a). Thereafter it has been developing and in the 1990s and 2000s a consensus of opinion was reached that it is an independent concept (Fried et al. 2001, Fried et al. 2004, Morley et al. 2006).

Decreased body reserves (Bergman et al. 2007, Strandberg & Pitkala 2007), decreased ability to counteract stressors (Bergman et al. 2007, Strandberg & Pitkala 2007, Clegg et al. 2013), and an increased risk of poor prognosis (Rockwood et al. 1994, Fried et al. 2001, Bortz 2002, Fried et al. 2004, Morley et al. 2006, Rockwood & Mitnitski 2007, Rolland et al. 2008, Fulop et al. 2010, Clegg et al. 2013) have been suggested to be characteristics of frailty. Frailty has been distinguished from disabilities and comorbidities (Fried et al. 2001, Fisher 2005), although it often appears with them at the same time (Fried et al. 2001). Figure 1 shows the relationship of frailty according to Fried criteria with comorbidities, and disabilities in the Cardiovascular Health Study: of frail participants, nearly half (46.2%) had comorbidities, 5.7% had disabilities, 21.5% had both comorbidities and disabilities, and about one quarter (26.6%) did not have comorbidities or disabilities (Fried et al. 2001).

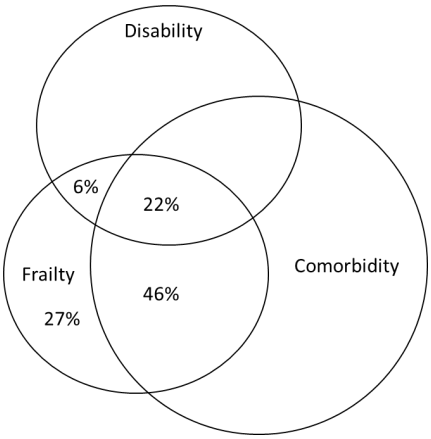

Figure 1. Venn diagram showing proportions of frail participants in respect to disability and comorbidity. Figure modified from the Cardiovascular Health Study (Fried et al. 2001).

However, we still lack an official definition of frailty (Fulop et al. 2010, Azzopardi et al. 2016). Populations are getting older and defining frailty is even more important than before (Rockwood 2005). For research a simple and clear definition would be practical as it would facilitate setting the research questions and also comparison of different studies (Fisher 2005). It is also important to define frailty to be able to recognize frail persons for early intervention and for prevention and treatment (Strandberg & Pitkala 2007).

2.1.1 DIAGNOSIS AND CLASSIFICATION

There have been many propositions for definitions of frailty. Two of them are widely used: the Fried criteria presenting the phenotype of frailty (Fried et al. 2001), and the Frailty Index (FI) presenting deficit accumulation criteria (Mitnitski et al. 2001).

2.1.1.1 Phenotype of frailty

Of the proposed definitions, the Fried criteria (Fried et al. 2001) and its modifications are most often used (Strandberg & Pitkala 2007). The Fried criteria stands for phenotype of frailty and are based on mobility parameters and weight change (Fried et al. 2001). The five Fried criteria are: unintentional weight loss, weakness, exhaustion, slow gait speed, and a low level of physical activity (Fried et al. 2001). A person is considered to be frail if at least three criteria are present, and prefrail if one or two criteria are present. If none of the criteria are present the person is considered to be robust (Fried et al. 2001). Table 1 summarizes the Fried criteria.

Table 1. The Fried criteria for the phenotype of frailty (Fried et al. 2001).

Criterion (if present, 1 pt)	Definition
Unintentional weight loss	>10 lbs (4.5 kg) in preceding year
Weakness	Lowest quintile in grip strength (by body mass index, gender)
Exhaustion	Self-reported exhaustion
Slow gait speed	Lowest quintile in walking speed (by height, gender)
Low physical activity	Lowest quintile in Kcals/week (males: <383 Kcals/week, females: <270 Kcals/week)
Frailty:	3–5 criteria present: frail; 1–2 criteria present: prefrail; 0 criteria present: robust

The Fried criteria have been widely used since 2001 (Strandberg et al. 2011) and they have predicted important outcomes such as disabilities and mortality (Fried et al. 2001, Bandeen-Roche et al. 2006). However, Fried criteria have also been criticized because they take into account only physical characteristics, ignoring biological, psychological and social aspects (Fisher 2005). On the other hand, use of physical criteria facilitates research (Fisher 2005).

2.1.1.2 Frailty Index (FI)

The Fried criteria are thought to be usable but there has been intense discussion on adding geriatric problems and cognitive capacity to the criteria of frailty (Rockwood et al. 2004, Rockwood 2005). If that were to be the case important geriatric aspects would be more comprehensively considered (Rockwood 2005). Frailty status is presumably different between two persons whose physical characteristics are similar but other features such as cognitive function are different (Rockwood 2005).

The FI is widely used and it takes into consideration features other than physical characteristics (Mitnitski et al. 2001, Fisher 2005). The FI is quantitative and is composed of various items (Mitnitski et al. 2001, Fisher 2005), usually 30–70 items (Song et al. 2010). These are various aspects of physical, cognitive, psychological and social dimensions (Mitnitski et al. 2001, Fisher 2005) such as motivation, communication, motion, balance, urinary and intestinal function, activities of daily living (ADL), nutrition, diseases, and social contacts (Mitnitski et al. 2001, Abellan van Kan et al. 2008a). The FI is calculated simply by dividing the number of deficits by the number of measured features (Mitnitski et al. 2001, Mitnitski et al. 2002). Thus, the FI gives a value between 0–1 in which 1 is for a person with all the measured deficits and 0 for a person with no deficits (Mitnitski et al. 2001, Mitnitski et al. 2002). The FI is a continuous measure of frailty (Mitnitski et al. 2001) but researchers have often used cut-off points of ≥0.25 to identify frail people and 0.08–0.249 to identify prefrail persons, whereas those scoring <0.08 are considered to be robust (Rockwood et al. 2004, Rockwood et al. 2007, Song et al. 2010). For example, persons with nine or more deficits in 36 items are considered to be frail, those with 3–8 deficits as prefrail, and those with 0–2 as robust.

The FI is significantly associated with mortality (Rockwood et al. 2007). It also enables evaluation of different study groups (Clegg et al. 2013). However, it is cumbersome to use in clinical work, and, thus, is not suitable in primary healthcare (Strandberg et al. 2011). It has been suggested that the Fried criteria and the FI are too different to be alternatives (Cesari et al. 2014). Instead, they could be used to complement and support each other (Cesari et al. 2014).

2.1.1.3 Other frailty measures

The phenotypic Fried criteria have been modified according to the study population and relevant data (Sirola et al. 2011). For example, a RAND-36 health survey questionnaire was used as a basis to construct the Helsinki Businessmen Study (HBS) frailty measure (Sirola et al. 2011). The HBS frailty measure is based on four criteria: weight loss (over 5% from midlife to senescence, or body mass index (BMI) <21 kg/m^2), physical weakness (self-reported difficulty in carrying a grocery bag), exhaustion (according to the

RAND-36 Vitality Scale from), and physical inactivity (not exercising regularly on a weekly basis) (Sirola et al. 2011). Those with 3–4 criteria present are considered frail, those with 1–2 criteria as prefrail, and those with no criteria as robust (Sirola et al. 2011).

The Women's Health Initiative Observational Study (WHI-OS) measure (Woods et al. 2005) is another measure with modified Fried criteria. It has the same criteria for unintentional weight loss and physical inactivity as in the HBS (Woods et al. 2005). Exhaustion is defined according to the RAND-36 Vitality Scale: "Did you feel worn out? Did you feel tired? Did you have a lot of energy? Did you feel full of pep?", with a score of <55 indicating the criterion is present. Slowness/weakness is evaluated as a two-point measure and the other three are single-point measures. Slowness/weakness is present if the score is <75 in the RAND-36 Physical Function Scale (Woods et al. 2005). Persons with 3–5 points are considered frail, those with 1–2 points as prefrail, and those with no points as robust (Woods et al. 2005).

The Study of Osteoporotic Fractures (SOF) frailty index is composed of three items: weight loss of ≥5% over three years, inability to rise from a chair five times without using arms, and reduced energy level (answer "no" to the question "Do you feel full of energy?" (Ensrud et al. 2008). Each of the three items is scored one point when present (Ensrud et al. 2008). According to the sum of points a person is classified as robust (0 points), prefrail (1 point), or frail (2 or 3 points) (Ensrud et al. 2008). The SOF frailty index predicted the risks of falls, fractures, disability, and death equally well as the more complex Fried's criteria (Ensrud et al. 2008).

The FRAIL scale is a simple 5-item questionnaire used to evaluate frailty (Abellan van Kan et al. 2008a, Abellan van Kan et al. 2008b). Each item is evaluated either as present (1 point) or not present (0 points) (Morley et al. 2012). Fatigue is evaluated as present with answers "All of the time" or "Most of the time" to the question "How much of the time during the past four weeks did you feel tired?" Resistance is evaluated as present with the answer "Yes" to the question "By yourself and not using aids, do you have any difficulty walking up ten steps without resting?" Ambulation is evaluated as present with the answer "Yes" to the question "By yourself and not using aids, do you have any difficulty walking several hundred yards?" Illnesses are evaluated as present when a person has 5 to 11 diseases of the 11 asked about (cancer [other than a minor skin cancer], chronic lung disease, hypertension, heart attack, congestive heart failure, angina, stroke, diabetes, asthma, kidney disease, and arthritis). Loss of weight is evaluated as present when over 5% in one year (Morley et al. 2012). The FRAIL scale is suitable for screening frail persons and it has been validated (Morley et al. 2012).

The Edmonton Frail Scale (EFS) assesses nine domains of frailty: general health status, cognition, social support, mood, continence, functional independence, functional performance, medication usage, and nutrition (Rolfson et al. 2006). These are evaluated by way of 11 items, of which six score 0, 1 or 2 points, and five score 0 or 1 point (Rolfson et al. 2006). Thus, the total

score is from 0 to 17, of which scores of ≤5 points refer to no frailty, scores of 6–11 refer to apparently vulnerable, and scores of 12–17 refer to severe frailty (Perna et al. 2017). The Edmonton Frail Scale is a valid, reliable and feasible frailty measure (Rolfson et al. 2006, Perna et al. 2017).

Winograd's frail scale classifies persons to three categories: independent people are those who are independent in all aspects of ADL, with short-term acute illness; frail people are those who meet any one of the assessed criteria (cerebrovascular accident, chronic and disabling illness, confusion, dependence in ADL, depression, falls, impaired mobility, incontinence, malnutrition, polypharmacy, pressure sores, prolonged bed-rest, restraints, sensory impairment, socioeconomic/family problems); severely impaired people are those who have severe dementia and ADL-dependence or have terminal illness (Winograd et al. 1991). Winograd's frail scale is inexpensive and effective and can easily be introduced into clinical settings (Winograd et al. 1991).

Even simpler measures have also been used to identify frail individuals (Morley et al. 2002). These include slow gait speed (if it takes over 10 seconds to walk three meters back and forth), "Timed Up and Go" test with a glass of water (if it takes over 4.5 seconds longer to walk three meters back and forth with a glass than without it), and abnormal balance on one foot (Morley et al. 2002). The advantage of these measures is that they are simple and cheap.

Gait speed over a 4-meter distance could be the most suitable test in clinical work to screen for frailty as it is not only cheap and simple but also reliable (Abellan van Kan et al. 2008a, Abellan van Kan et al. 2009). A gait speed of ≤0.6 m/s predicts failing in a 400-meter walking test (Rolland et al. 2004), passing of which is considered to be crucial to maintain independence and a high quality of life in the community (Pahor et al. 2006, Pahor et al. 2014).

Fried criteria have also been modified so as to be able to screen for frailty status in the population via questionnaire investigations (Woods et al. 2005, Etman et al. 2012).

2.1.2 EPIDEMIOLOGY OF FRAILTY

A systematic review revealed that the prevalence of frailty varies widely, from 4.0% to 59.1% among community-dwelling persons (Collard et al. 2012). Taking into account all the studies in the review, 10.7% of the persons were frail and 41.6% were prefrail (Collard et al. 2012). In one study of community-dwelling participants the prevalence was over ten times higher among 90-year-old (56.3%) than among 65-year-old (4.8%) persons (Brody et al. 1997).

The lack of consensus on an official definition of frailty is one reason for different prevalence rates in various studies (Bortz 2002, Fried et al. 2004, Strandberg et al. 2011, Collard et al. 2012). Studies involving use of the FI usually present a higher prevalence of frailty than those involving the use of phenotype-based measures (Fried et al. 2001, Song et al. 2010, Jurschik et al. 2012, Malmstrom et al. 2014, Kojima et al. 2015, Widagdo et al. 2015). The

prevalence is also affected by the characteristics of the study population (Fried et al. 2001, Strandberg et al. 2011). The prevalence of frailty increases with age (Fried et al. 2001, Song et al. 2010, Strandberg et al. 2011, Collard et al. 2012). Females are more often frail than males (Fried et al. 2001, Song et al. 2010, Collard et al. 2012). Lower socioeconomic status, diseases, disabilities and institutionalization increase the prevalence of frailty (Fried et al. 2001, Strandberg et al. 2011). Both poor psychological and financial well-being have also been associated with frailty (Hubbard et al. 2014).

Frailty and dementia share some risk factors such as smoking, obesity, low-level physical activity, and depression, and it has been suggested that they increase each other's prevalence (Sampson 2012). Many studies have shown a higher prevalence of dementia among frail persons than among prefrail or robust persons (Robertson et al. 2013). Both cognitive impairment and dementia are common among frail persons (Avila-Funes et al. 2009, Jurschik et al. 2012). A systematic review and meta-analysis revealed frailty to be a significant predictor of dementia among community-dwelling older people (Kojima et al. 2016a). One study on frailty in AD patients revealed 22% to be robust, 28% to be prefrail and 50% to be frail (Bilotta et al. 2012). The frail persons also had more severe degrees of cognitive impairment (Bilotta et al. 2012).

Table 2 presents the prevalence of frailty in various studies with different frailty measures in community-dwelling older adults and among people with dementia.

Table 2. Prevalence of frailty in various studies.

Study, country	N	Mean age or range	Female	Criteria for frailty/ dementia	Prevalence
Among community-dwelling persons					
Fried et al. 2001, USA	5317	65–74 years: 67.3% 75–84 years: 29.1% 85+ years: 3.6%	58%	Fried	Frail 6.9%, prefrail 46.6%
Woods et al. 2005, USA	40,657	65–69 years: 47.6% 70–79 years: 52.4%	100%	Modified Fried	Frail 16.3%, prefrail 28.3%
Cawthon et al. 2007, USA	5993	73.7 years	0%	Fried	Frail 4.0%, prefrail 40.0%
Avila-Funes et al. 2008, France	6078	74.1 years	61%	Fried	Frail 7.0%, prefrail 47.6%
Gallucci et al. 2009, Italy	668	84.1 years	53%	Rising from a chair and walking speed	Frail 16.3%, prefrail 39.2%
Chen et al. 2010, Taiwan	2238	73.3 years	49%	Fried	Frail 4.9%, prefrail 40.0%
Song et al. 2010, Canada	2740	74.0 years	61%	FI (from self-reported data)	Frail 22.7%
Sirola et al. 2011, Finland	1125	73.3 years	0%	Modified Fried	Frail 9.6%, prefrail 50.4%
Etman et al. 2012, 11 European countries	14,424	55–59 years: 23.9% 60–64 years: 21.6% 65–69 years: 19.2% 70–74 years: 15.0% 75–79 years: 11.1% 80+ years: 9.3%	54%	Modified Fried	Frail 8.8%, prefrail 39.1% at the beginning
Jurschik et al. 2012, Spain	640	81.3 years	60%	Fried	Frail 9.6%, prefrail 47%
Malmström et al. 2014, USA	779	56.3 years	Not mentioned	Modified Fried, FI ≥0.25 (25 items)	Fried Frail 6.3%, Fried Prefrail 51.6%, FI Frail 22.6%
Kojima et al. 2015, United Kingdom	248	72.9 years	64%	FI ≥0.25 (40 items)	Frail 18.5%
Widagdo et al. 2015, Australia	2087	78.2 years	49%	Modified Fried, FI ≥0.25 (39 items)	Fried Frail 8.8%, Fried prefrail 57.7%, FI Frail 17.5%
Lee et al. 2016, USA	824	90–94 years: 73.9% 95+ years: 26.1%	72%	Modified Fried	Frail 28.0%
Zheng et al. 2016, China	10,039	70.5 years	61%	FI ≥0.25 (34 items)	Frail 12.3%

Table 2. Continued…

Study, country	N	Mean age or range	Female	Criteria for frailty/ dementia	Prevalence
Among persons with Alzheimer disease					
Bilotta et al. 2012, Italy	109	82.8 years	77%	Modified SOF/ DSM-IV	Frail 49.5%, Prefrail 27.5%, Robust 22.9%
Kulmala et al. 2014, Finland	97	82 years	69.6%	Modified Fried/ DSM-IV	Frail 28.9%, Prefrail 47.4%, Robust 23.7%
Oosterveld et al. 2014, Netherlands	213	75 years	58%	Modified Fried/ NINCDS-ADRDA	Frail 11.1%, Prefrail 49.3%, Robust 39.6%
Tay et al. 2016, Singapore	83	76.6 years	65%	Modified Fried/ NINCDS-ADRDA	Frail 21.7%, Prefrail -, Robust 78.3%

DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, IVth edition; FI=Frailty Index (Mitnitski et al. 2001); Fried=Fried frailty criteria (Fried et al. 2001); NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association; SOF=Study of Osteoporotic Fractures frailty measure (Ensrud et al. 2008)

2.1.3 BIOLOGICAL BASIS OF FRAILTY

Both inflammatory and coagulative alterations have been suggested to play a part in the pathogenesis of frailty (Kanapuru & Ershler 2009). Aging is associated with changes in the amounts of cytokines, resulting in a decrease of body reserves (Fulop et al. 2010). In developing frailty there are similar but stronger changes resulting in the clinical frailty syndrome (Fulop et al. 2010). Increased interleukin 6 (IL-6) concentrations have shown the strongest association with frailty (Fulop et al. 2010), and other associated cytokines are C-reactive protein (CRP), tumor necrosis factor α (TNF-α), and ligand 10 of the CXC chemokine family (CXCL10) (Walston et al. 2006, Clegg et al. 2013).

It has been argued that most human organs have an approximately 70% margin, meaning that 30% function of the total capacity is enough to support normal function (Bortz 2002). The pathogenesis of frailty includes decreases of reserves in multiple body organs, for example in the digestive system, muscles, bones, circulatory system, the brain, and the immune system, and depressed hormone function (Fried et al. 2004, Abellan van Kan et al. 2008a). Various frailty-related diseases and symptoms include anorexia, weight loss, sarcopenia, osteopenia, atherosclerosis, congenital impairment, exhaustion, hormone deprivation and reduced inflammatory reactions (Strandberg et al. 2011). In frailty, some body reserves are decreased close to the 30% margin, after which it may be difficult to compensate for even a small disturbance in body or environment (Fried et al. 2001, Fried & Walston 2003, Fried et al. 2004).

Figure 2 shows possible relationships between molecular, physiological and functional factors related to frailty (Walston et al. 2006, Fulop et al. 2010).

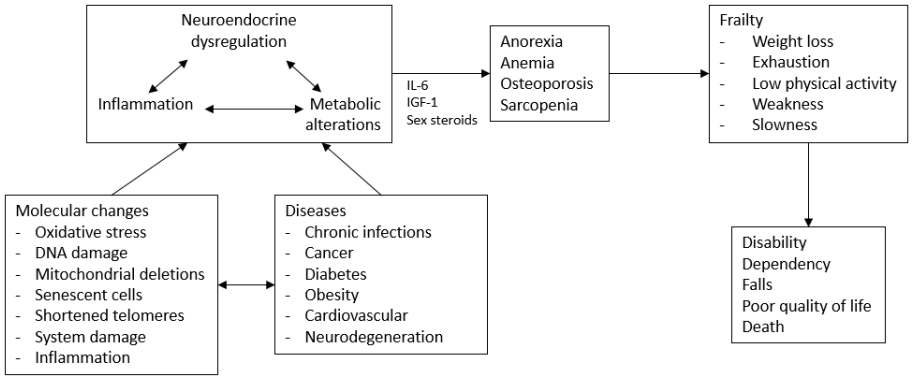

Figure 2. Hypothesis of mechanisms in the development of frailty (IGF-1: insulin-like growth factor 1; IL-6: interleukin 6).

2.1.4 RISK FACTORS AND ASSOCIATED FACTORS OF FRAILTY

The development of frailty is associated with genetic, biological, physical, psychological, social, and environmental domains (Rockwood & Mitnitski 2007). Four entities have been thought to be the most important: genetic properties, aging, lifestyles, and outcomes of diseases and traumas (Bortz 2002, Fried et al. 2004).

Female gender provides an example of genetic influence (Fried et al. 2001). Frailty prevalence is higher among women than among men, and a major factor is that muscle mass and power are lower and they decrease faster among women (Fried et al. 2001). Menopause hastens the development of frailty (Nedergaard et al. 2013). Some genetic disorders may also contribute to the development of frailty, but they occur in a minor proportion of the total frail population (Bortz 2002).

The amount of muscle tissue decreases with age (Hughes et al. 2002). A decrease in nutritional intake along with reduced exercise results in decreased muscle mass (Morley 2001). Aging also brings possible accumulation of metabolic byproducts, stiffness of muscle fascia and changes in DNA, causing muscle weakness (Bortz 2002). However, aging is probably not itself the reason for loss of muscles, as not all persons lose muscles in aging (Fiatarone et al. 1990). A widely accepted functional aspect of aging is a situation in which the physiological reserves cannot cope with any disturbances although they function normally in a steady state (Fulop et al. 2010). When reserves have decreased to the marginal 30% level along with aging and the body faces a factor disturbing the steady state it may be argued that aging strongly contributes to the development of frailty (Fulop et al. 2010). However, aging and frailty are two different entities, as not all people become frail even when they are very old (Strandberg et al. 2011). Aging does not cause frailty but is a predisposing factor (Strandberg et al. 2011).

Lifestyles are thought to be the most important factor in the development of frailty (Bergman et al. 2007). Lifestyles at an advanced age have an effect but they are also important in middle age and even in youth (Savela et al. 2013).

Exercise during the whole course of life has shown benefits in preventing frailty (Savela et al. 2013). The participants of the Helsinki Businessmen Study were divided into three groups based on their exercise activity in their middle age: low, moderate, and high (Savela et al. 2013). High-level physical activity in leisure time in middle age predicted a significantly lower prevalence of frailty or prefrailty 26 years later at an advanced age (Savela et al. 2013). A sedentary life style leads to decreased muscle power and frailty (Bortz 2002). This is supported by many studies demonstrating an association between insufficient exercise and muscle degradation in later decades of life (Bortz 2002).

As regards nutrition the problem is getting enough energy and especially enough protein in advanced age, whereas in youth and middle age the problem is getting too much energy (Morley 2007). Too much nutritional energy intake

causes obesity, type 2 diabetes mellitus, and cardiovascular diseases (Strandberg et al. 2013a, Strandberg et al. 2013b, Stenholm et al. 2014). These conditions are also associated with insufficient exercise (Savela et al. 2013) and smoking (Strandberg et al. 2008). Smoking shortens life and also quality-adjusted life years (QALY) and is associated with frailty (Strandberg et al. 2008, Hubbard et al. 2009). The development of frailty may thus begin in early middle age and obesity is one etiologic factor (Stenholm et al. 2014). It has been reported that both those remaining overweight and those reducing weight from obesity to a normal weight level over 26 years were more frail and had more disabilities and poorer prognoses compared with those staying at a normal weight (Strandberg et al. 2013b). The risk of frailty is also increased by alcohol intake, metabolic syndrome, and certain diseases such as diabetes, atherosclerosis, and infections (Strandberg et al. 2011).

The above-mentioned chronic diseases themselves cause chronic inflammation and also predispose individuals to acute diseases (Fulop et al. 2010). The effects of diseases and traumas are at least partly explained by reduced exercise levels (Toth & Poehlman 2000). This reduces muscle mass, which in turn accelerates the decrease of body reserves (Clegg et al. 2013). With lack of reserves the body is more vulnerable to disturbances (Fulop et al. 2010). Inflammation is associated with frailty (Ferrucci et al. 2002, Roubenoff 2003) because it disturbs the functions of various organ systems via cytokine action (Fulop et al. 2010). The term secondary frailty is used when diseases have had a major impact in its development and the term primary frailty is used in the absence of such contributing diseases (Strandberg & Pitkala 2007).

2.1.5 OUTCOMES OF FRAILTY

Frailty has a poor prognosis (Rockwood & Mitnitski 2007). It leads to disabilities, complications and an increased risk of death (Rockwood et al. 1994, Fried et al. 2001, Bortz 2002, Fried et al. 2004, Morley et al. 2006, Rockwood & Mitnitski 2007, Rolland et al. 2008, Fulop et al. 2010). Prefrailty also predisposes persons to diseases and disabilities, exacerbating their consequences and making it more difficult to recover from acute illnesses (Fried et al. 2001). According to a systematic review and meta-analysis both prefrailty and frailty are significant predictors of fractures among community-dwelling older people (Kojima 2016).

Frailty more often worsens than evolves towards a better condition (Fried et al. 2001). In the Cardiovascular Health Study (CHS) mortality was higher among frail (18%) than among prefrail (7%) or robust (3%) persons after three years of follow-up as well as after seven years of follow-up (43%, 23%, 12%, respectively) (Fried et al. 2001). Frailty remained as an independent risk factor of falls, institutionalization, and increased rates of disabilities and mortality after adjusting for socioeconomic level, health status, clinical and subclinical diseases, depression symptoms and present disabilities (Fried et al. 2001). The prefrail group showed more than a 2.5-fold increased risk of developing frailty

during 3–4 years of follow-up compared with the robust group (Fried et al. 2001). In the Helsinki Businessmen Study the mortality rate during seven years of follow-up showed similar figures: 39% in the frail group, 19% in the prefrail group, and 8% in the robust group (Sirola et al. 2011). Both frailty and prefrailty predicted mortality after adjusting for [OK?] age, BMI, smoking, frailty phenotype criteria, the Charlson comorbidity index and mobility disabilities (Sirola et al. 2011).

2.1.6 PREVENTION AND MANAGEMENT OF FRAILTY

Reducing the prevalence and severity of frailty probably benefits both individuals and society (Clegg et al. 2013). The prevention of frailty should begin early, focusing on lifestyles (Strandberg et al. 2011), as they are thought to be a major factor in developing frailty (Bergman et al. 2007) and because lifestyles in early adulthood and even in youth may contribute to its development (Savela et al. 2013).

Lifelong exercise training and physical activity prevent frailty (Savela et al. 2013). As several studies have revealed muscle weakness to be associated with increased mortality and to contribute to frailty development, exercise training provides a simple means of prevention and rehabilitation (Bortz 2002). Over-nutrition and overweight should be avoided in youth and middle age, whereas at a more advanced age sufficient energy intake (especially protein intake) prevents frailty (Morley 2007). Efficient treatment of diseases and traumas decreases the risk of frailty (Strandberg et al. 2011). Early mobilization and adequate nutrition in acute illnesses is important, especially among older people (Strandberg et al. 2011). Probable preventive factors against frailty include healthy nutrition, nonsmoking, moderate alcohol consumption and taking care of overall health status (Bergman et al. 2007). Vaccines developed against both acute and chronic infections may decrease chronic inflammation and frailty (Fulop et al. 2010).

Several different forms of intervention have been studied to reduce frailty (Clegg et al. 2013). Intervention measures have consisted of exercise, nutrition and pharmacological intervention, as well as different combinations of these (Strandberg et al. 2011, Clegg et al. 2013). Exercise intervention has shown the most evidence of effectiveness (Walston et al. 2006, Strandberg et al. 2011). In a systematic review it was suggested that frail older adults seem to benefit from exercise interventions (de Labra et al. 2015). A meta-analysis revealed exercise training to benefit frail older people in respect of enhancing gait speed, balance and ADL (Chou et al. 2012). Another systematic review on exercise in frailty revealed that only three out of 47 studies had defined frailty according to a valid definition (Theou et al. 2011). There is strong evidence that exercise enhances functionality of the heart, respiratory system and muscles, and physical activity and functional ability (Theou et al. 2011). There is also moderate evidence that exercise is of benefit in psychological and biochemical domains, as well as decreasing adverse outcomes (Theou et al. 2011). A

diverse, long-term (more than five months) program of exercise training, 30–45 minutes three times a week has benefited the most (Theou et al. 2011). A diverse mixture of strength, endurance and balance training seems best to reduce falls and enhance gait and physical function in physically frail older people (Cadore et al. 2013b). A 12-week circuit-training program has reduced the fear of falling and enhanced health status among physically frail older people (Gine-Garriga et al. 2013). A study on exercise, dietary supplementation and both of these showed only exercise to benefit frail older people (Fiatarone et al. 1994). Exercise interventions may benefit prefrail more than frail persons (Faber et al. 2006).

Nutritional interventions may enhance nutritional status and prevent weight loss in frailty, but there is scarce evidence (Clegg et al. 2013). Protein and energy supplements enhance weight gain but do not affect the ability to function among older people (Milne et al. 2009). Nutritional interventions based on energy supplementation have not been efficient in frailty (Walston et al. 2006). However, a daily protein supplement for 12 weeks reduced the worsening of functional decline among frail older people of relatively low socioeconomic status (Kim & Lee 2013).

Only a few pharmacological means have been investigated in the management of frailty (Clegg et al. 2013). For example, erythropoietin, angiotensin-converting enzyme inhibitors (ACE inhibitors) and statins have shown benefits that could possibly be used to prevent and manage frailty, but there is no clear evidence of benefits in functional ability (Walston et al. 2006). In clinical trials anabolic steroids such as testosterone and dehydroepiandrosterone (DHEA) increased muscle mass but they did not increase muscle functionality without exercise training (Walston et al. 2006). Side effects limit their use (Walston et al. 2006). However, pharmacological agents in the prevention and management of frailty remain an important topic in future studies (Clegg et al. 2013).

An intervention study on exercise and nutrition combined led to a decrease in frailty stage (from frail to prefrail/robust or from prefrail to robust) in three months, compared with a control group (Chan et al. 2012). However, this change was no longer evident after six and twelve months of follow-up (Chan et al. 2012). Another intervention study combining exercise with nutritional and psychological care showed that the intervention group had a significantly higher gait speed and activity level than a control group (Fairhall et al. 2012).

It seems that interventions benefit the frailest less than prefrail persons (Beswick et al. 2008). Advancing memory diseases are known to predispose people to frailty (Sampson 2012). However, there is lack of studies concerning how to slow down the progression to frailty among persons with dementia (Sampson 2012).

Intervention studies are presented in Table 5 (below, in Section 2.3.1, Exercise interventions in frailty).

2.2 FALLS

Falls and injuries increase with age (Campbell et al. 1990, Rubenstein & Josephson 2002). Risk factors of falls have been studied extensively in older populations in general, but there are fewer studies on risk factors of falls among people with dementia (Allan et al. 2009, Salva et al. 2012, Meuleners et al. 2016). Persons with cognitive impairment and dementia are at major risk of falls (Tinetti et al. 1988, van Dijk et al. 1993).

2.2.1 DEFINITION OF A FALL

A fall has been defined in various ways (Hauer et al. 2006). A widely used definition proposed in 1987 described a fall as "unintentionally coming to the ground or some lower level and other than as a consequence of sustaining a violent blow, loss of consciousness, sudden onset of paralysis as in stroke or an epileptic seizure" (Kellogg 1987). Later, a simpler definition was suggested, being "an unexpected event in which the participants come to rest on the ground, floor, or lower level" (Lamb et al. 2005). A systematic review by the Prevention of Falls Network Europe group revealed that only half of randomized controlled fall-prevention trials had defined a fall, hence impeding comparison between different studies (Hauer et al. 2006). On the other hand, an answer to a simple question "Did you fall?" has been suggested to fulfill clinical and epidemiological purposes with adequate accuracy (Dickens et al. 2006). A comprehensive, non-exclusive and simple fall definition to be reliably understood by lay people documenting their falls is recommended (Hauer et al. 2006).

2.2.2 EPIDEMIOLOGY OF FALLS

Approximately one of three community-dwelling persons aged over 65 years falls every year (Tinetti et al. 1988, Rubenstein & Josephson 2002). The incidence of falls as well as the severity of complications rise after the age of 60 years (Campbell et al. 1990, Rubenstein & Josephson 2002, Milat et al. 2011). The incidence is higher among nursing-home residents than among those living in the community (Becker et al. 2003). Women fall more than men (Deandrea et al. 2010). The incidence of falls varies according to the type of population, e.g. persons with Parkinson disease fall more often (Deandrea et al. 2010).

Frailty is a major risk factor of falls (Samper-Ternent et al. 2012). Several studies have shown that frail persons fall more than prefrail and robust persons (Runzer-Colmenares et al. 2014, Zaslavsky et al. 2016). The proportions of fallers have usually varied from 20% to 80% among frail persons (Ensrud et al. 2009, Runzer-Colmenares et al. 2014). Frailty also predisposes people to recurrent falls (Bandeen-Roche et al. 2015).

Cognitive impairment and dementia are major risk factors of falls, as approximately 60% of older persons with these disorders fall annually (Tinetti et al. 1988, van Dijk et al. 1993). Fewer fallers have also been reported, as a Japanese study among AD participants revealed 42% (Horikawa et al. 2005) and a Spanish study among dementia participants revealed 36% (Salva et al. 2012) to fall during one-year of follow-up. In contrast, a UK study among dementia participants revealed 66% to fall during one-year of follow-up (Allan et al. 2009). The type of dementia affects the number of fallers (Allan et al. 2009). During one-year follow-up the percentages of fallers were 47% for those with AD, 47% for those with vascular dementia, 77% for those with dementia with Lewy bodies and 90% for those with Parkinson's disease with dementia (Allan et al. 2009).

Table 3 presents the incidence of falls in various studies among community-dwelling persons, among frail persons, and among persons with dementia.

Table 3. Epidemiology of falls among community-dwelling older people, among persons with frailty, and among persons with dementia.

Study, country	N	Age	Female	Criteria for frailty/ dementia	Fallers, %
Among community-dwelling persons					
Tinetti et al. 1988, USA	336	Mean 78.4 years	55.1%	N.A.	Follow-up 12 months, 32.1%
Zimba Kalula et al. 2015, South Africa	632	Mean 75 years	77.2%	N.A.	Follow-up 12 months: Fallers: 21.9% Recurrent fallers: 6.3%
Gale et al. 2016, United Kingdom	4301	60–69 years: 2321 70–79 years: 1538 80+ years: 442	54.8%	N.A.	Fallers during 24 months: 28.4%
Verma et al. 2016, USA	20,752	A sample of 18+ year old U.S. citizens living in the community	Not mentioned	N.A.	Fallers in age groups during 12 months: 18–44: 10.6% 45–64: 11.4% 65+: 16.4%
Among frail persons					
Ensrud et al. 2007, USA	1045	Mean 79.9 years	100%	Fried	Follow-up 12 months, 20% had ≥2 falls
Ensrud et al. 2009, USA	Fried: 432 SOF: 411	Mean 76.4 years	0%	Fried, SOF	Follow-up 12 months (≥2 falls) Fried: 28.2% SOF: 27.0%
Samper-Ternent et al. 2012, USA	847 Frail 105 Prefrail 416 Not Frail 326	Mean 82.0 years	64.7%	Fried	Fallen during 12 months: Frail 54.3% Prefrail 49.0% Not Frail 40.2%
Runzer-Colmenares et al. 2014, Peru	311 (hospital based cohort) Frail 86 Prefrail 147 Non-frail 78	Mean 76.1 years	40.5%	Modified Fried	Fallen last year: Frail 77.9% Prefrail 59.2% Non-frail 57.7%

Table 3. Continued…

Study, country	N	Age	Female	Criteria for frailty/ dementia	Fallers, %
Bandeen-Roche et al. 2015, USA	7439 Frail 15.3% Prefrail 45.5% Robust 39.2%	65–69 years: 28.1% 70–74 years: 25.0% 75–79 years: 19.1% 80–84 years: 14.6% 85–89 years: 9.0% 90+ years: 4.2%	56.4%	Fried	Fallen during 12 months: Frail 54.9% Prefrail 32.9% Robust 18.1% Fallen ≥2 times last year: Frail 35.2% Prefrail 13.8% Robust 5.0%
Zaslavsky et al. 2016, USA	3558 Frail: 172 Prefrail: 1847 Nonfrail 1539	Mean 70.9 years	100%	Fried	Mean follow-up of 12 years (Incidence/1000 person-years) Frail: 146.1 Prefrail: 111.0 Nonfrail: 104.5
Among persons with dementia					
Horikawa, et al. 2005, Japan	124 AD persons, MMSE mean 16.2	Mean 74.1 years	72.1%	NINCDS-ADRDA	Fallen during 12 months of follow-up: 42.3%
Allan et al. 2009, United Kingdom	179 from outpatient clinics AD 38 VAD 32 DLB 30 PDD 40 Controls 39	Means: AD: 79 years VAD: 79 years DLB: 76 years PDD: 72 years Controls: 75 years	AD 52.6% VAD 28.1% DLB 40.0% PDD 35.0% Controls 46.2%	DSM-IV	Falls/1000 pyrs: AD 2486 VAD 3135 DLB 9087 PDD 19000 Controls 1023
Salva et al. 2012, Spain	626 community-dwelling persons with dementia, MMSE mean 15.9	Mean 78.6 years	68.5%	Various types of dementia, criteria not mentioned	Fallen during 12 months of follow-up: 35.6%

AD=Alzheimer Disease; DLB=Dementia with Lewy bodies; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders; Fried=Fried frailty criteria (Fried et al. 2001); MMSE=Mini-Mental State Examination (Folstein et al. 1975); N.A.=Not applicable; NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association; PDD=Parkinson's disease with dementia; pyrs=person-years; SOF=Study of Osteoporotic Fractures frailty measure (Ensrud et al. 2008); VAD=Vascular Dementia

2.2.3 RISK FACTORS AND ASSOCIATED FACTORS OF FALLS

Risk factors of falls have been extensively investigated in older persons in the general population. Well-known risk factors are, for example, a history of falls, gait deficits, muscle weakness, disability, visual deficit, arthritis, depression, older age, polypharmacy, psychotropic medication, and environmental hazards (Tinetti et al. 1988, Campbell et al. 1999, Leipzig et al. 1999, AGS 2001, Stalenhoef et al. 2002, AGS 2011).

There are many risk factors of falls in various domains such as sociodemographic factors, medical factors, psychological factors, medication-related factors, and mobility and sensory factors (Deandrea et al. 2010). Risk factors can also be classified as intrinsic factors (e.g. balance disorder, poor grip strength, functional and cognitive impairment), extrinsic factors (e.g. polypharmacy) and environmental factors (e.g. lack of bathroom safety equipment, poor lightning) (AGS 2001).

Several drug classes and polypharmacy expose older people to the risk of falls (AGS 2011) and the use of psychotropic drugs is especially associated with falls among older people (Hartikainen et al. 2007, Woolcott et al. 2009). Furthermore, drugs with anticholinergic properties (DAPs) are associated with an increased frequency of falls (Cardwell et al. 2015, Mayer et al. 2017), and antihypertensive drugs have also been associated with an increased risk of falls (Hartikainen et al. 2007, Woolcott et al. 2009) and hip fractures (Corrao et al. 2015). A systematic review of 74 prospective studies revealed the strongest risk associations to be a history of falls (Odds Ratio [OR] = 3.5 for recurrent fallers; OR = 2.8 for all fallers), gait problems (OR = 2.2; 2.1), walking-aid use OR = 3.1; 2.2), vertigo (OR = 2.3; 1.8), Parkinson's disease (OR = 2.8; 2.7), and antiepileptic drug use (OR = 2.7; 1.9) (Deandrea et al. 2010). Other moderately associated factors were age, female gender, living alone, physical activity limitation, physical disability, instrumental disability, cognition impairment, depression, history of stroke, urinary incontinence, rheumatic disease, hypotension, diabetes, comorbidity, self-perceived poor health status, pain, fear of falling, increase in number of types of medication, use of sedatives, use of antihypertensives, vision impairment, and hearing impairment (Deandrea et al. 2010).

Frailty itself increases the risk of falls (Ensrud et al. 2007, Kojima et al. 2015). Frail persons have shown similarities with community-dwelling older persons in the general population in respect of risk factors of falls. For example, older age, certain diseases such as cardiovascular diseases and depression, and malnutrition have been shown to increase the risk of falls among frail persons (Ng et al. 2014).

Cognitive impairment and dementia are themselves major risk factors of falls, leading to approximately 60% of older people with these disorders falling annually (Tinetti et al. 1988, van Dijk et al. 1993). There are fewer studies on

fall-risk factors among persons with dementia, but a history of falls, older age, female gender and disability have been associated with increased risk (Allan et al. 2009, Salva et al. 2012, Meuleners et al. 2016). Furthermore, symptomatic orthostatic hypotension and symptoms of depression have been shown to increase the risk of falls, whereas higher levels of physical activity appeared to be protective against falls (Allan et al. 2009). More severe cognitive decline has been associated with an increased risk of falls (Gleason et al. 2009, Ohman et al. 2016). The use of psychotropic drugs has also been associated with an increase in the risk of falls among persons with dementia (Horikawa et al. 2005, Kudo et al. 2009).

2.2.4 OUTCOMES OF FALLS

The number of falls and adverse outcomes as results of a fall increase with age (Campbell et al. 1990, Rubenstein & Josephson 2002). Falls lead to substantial rates of mortality and morbidity and they are major contributors to immobility and premature nursing home placement (AGS 2001, Rubenstein 2006). Women are more likely to be injured as a consequence of falls than men (Duckham et al. 2013). One in four fallers faces serious injury, and approximately 6% have fractures such as a hip fracture and its possible adverse consequences (Tinetti et al. 1988). Minor injuries are more common and may be present in two-thirds of fallers (Milat et al. 2011). In the same study 20% of fallers required a hospital visit, half of them requiring hospital admission (Milat et al. 2011). Falls also result in major costs to society (Scuffham et al. 2003). These costs increase with age and the two highest costs have been reported to be from inpatient admissions (49%) and long-term care (41%) (Scuffham et al. 2003).

2.2.5 PREVENTION OF FALLS

Effective fall prevention has the potential to reduce emergency department visits, serious fall-related injuries, hospitalizations, nursing-home placements, and functional decline among older community residents (Sattin 1992). Reducing fall risk among older individuals is an important public-health objective (Sattin 1992).

A wide body of evidence supports a multifactorial or multicomponent approach to interventions designed to prevent falls in older persons (Chang et al. 2004, Weatherall 2004). Much evidence supports the fact that exercise interventions benefit older people in reducing fall risk (Campbell et al. 1999, Chang et al. 2004, Gillespie et al. 2012, Guirguis-Blake et al. 2018), and an exercise component should be included in all multifactorial interventions (AGS 2011). However, multifactorial interventions may offer only small net benefits compared with interventions consisting of only exercise (Grossman et al. 2018). In most positive trials exercise intervention has lasted at least 12 weeks (AGS 2011).

Possible medication reduction benefits older people in respect of fall prevention (AGS 2011). In particular, reduction of psychotropic medication has been found to reduce the fall rate (Campbell et al. 1999, Leipzig et al. 1999). Vitamin D supplementation has beneficial effects in fall prevention (Bischoff-Ferrari et al. 2009). Management of home hazards as a single form of intervention has shown mixed results (AGS 2011), but is of benefit in reducing falls when combined with exercise intervention (Day et al. 2002).

Falls have also been investigated in connection with frailty (Faber et al. 2006). Various studies have shown mixed results, as one study showed no benefits from exercise intervention (Latham et al. 2003) whereas another revealed that an exercise intervention group improved in respect of physical functioning and falls (Cadore et al. 2013a). In one study exercise intervention reduced the risk of becoming a faller among prefrail participants but increased the risk of becoming a faller among frail participants (Faber et al. 2006).

Although people with dementia are at an increased risk of falls, there has been a scarcity of studies investigating prevention of their falls (AGS 2011). Just recently, the results of a meta-analysis including seven studies suggested that exercise has the potential to prevent falls among people with known cognitive impairment (Chan et al. 2015). In a small study of persons with a mean Mini-Mental State Examination (MMSE) score of 16.3 the intervention group improved in walking, mobility, flexibility and static balance compared with the control group (Toulotte et al. 2003). Another study showed improvement in a multicomponent exercise intervention group, with a slower decline in ADL score and higher gait speed among persons with AD and a mean MMSE score of 8.8 (Rolland et al. 2007). There are also studies that have revealed no reduction in falls via exercise intervention among persons with dementia (Wesson et al. 2013). To my knowledge, there are no studies prospectively exploring the characteristics and consequences of falls among persons with dementia.

Table 4 presents fall prevention trials among community-dwelling persons, frail persons, and people with dementia.

Table 4. Exercise intervention trials to prevent falls among community-dwelling older people, among persons with frailty, and among persons with dementia.

Study, country	Participants	Intervention	Results
Among community-dwelling persons (meta-analyses)			
El-Khoury et al. 2013	17 trials, N=4305 Mean age 76.7 years Female 77% ≥60 years, Community-dwelling	IGs: HE, GE	IGs showed 37% reduction in all injurious falls, 43% in severe injurious falls, and 61% in falls resulting in fractures.
Lomas-Vega et al. 2017	10 studies, N=2621 Mean age and gender % not reported	IG: Tai Chi, 60 min, 1–3/wk, 12–26 wk	IG: fall risk reduction of 43% at short-term follow-up (<12 months) and fall-risk reduction of 13% at long-term follow-up (≥12 months).
Sherrington et al. 2017	88 trials, N=19,478 Mean age and gender % not reported	99 various interventions	Exercise reduced the rate of falls in community-dwelling older people by 21%.
Tricco et al. 2017	283 RCTs, N=159,910 Mean age 78.1 years Female 74% ≥65 years, all settings	77 various interventions to reduce number of fallers, and 39 various interventions to reduce injurious falls in included RCTs.	Exercise alone and various combinations including exercise reduced the number of fallers and the risk of injurious falls.
Among frail persons			
Latham et al. 2003, Australia, New Zealand	N=243 Mean age 79.1 years Female 53% Teaching hospitals, Winograd	IG1: HE, 3/wk, 10 wk CG1: therapist visits to home IG2: single oral dose of calciferol 300,000 IU CG2: single dose of placebo tablets Follow-up of 6 months.	No benefits in IG1 or IG2. IG1 had increased risk of musculoskeletal injury.
Faber et al. 2006, Netherlands	N=278 Mean age 85 years Female 79% In long-term care, modified Fried criteria	Both IGs: GE, 60 min training, 1–2/wk, 20 wk IG1: Functional walking group: exercises related to daily mobility activities IG2: In balance: 7 exercises by the principles of Tai Chi CG: No activity	Intervention reduced the risk of become a faller and improved physical performance among prefrail participants. Intervention increased the risk of becoming a faller among frail participants.
Cadore et al. 2013a, Spain	N=24 Mean age 91.9 years Female 70% Institutionalized, Fried	IG: 40 min, 2/wk, 12 wk CG: usual care	IG: improved in respect of physical functioning and falls.

Table 4. Continued…

Study, country	Participants	Intervention	Results
Among persons with dementia			
Shaw et al. 2003, United Kingdom	N=274 Mean age 84 years Female 80% Mean MMSE 13	IG: HE, session duration and times/wk not mentioned, 12 wk + multifactorial assessment medical and occupational items CG: usual care	No significant difference in the number of falls between groups.
Toulotte et al. 2003, France	N=20 Mean age 81.4 years Female not mentioned Mean MMSE 16.3 Persons with at least 2 previous falls. Only 5 subjects were classified as having a specific disease.	IG: GE, 45 min, 2/wk, 16 wk CG: daily routine	IG improved in walking, mobility, flexibility and static balance. IG had no falls during the 16 wk, whereas CG had 6 falls altogether.
Rolland et al. 2007, France	N=134 Mean age 83.0 years Female 75% Mean MMSE 8.8 Patients with AD living in nursing homes	IG: GE, 60 min, 2/wk, 12 months CG: routine medical care	IG had slower decline in ADL score and higher gait speed. No significant difference in the number of falls between IG and CG.
Pitkala et al. 2013, Finland	N=210 Mean age 78.0 years Female 39% Mean MMSE 18	Both IGs: 60 min, 2/wk, 12 months IG1: HE, individually tailored IG2: GE CG: usual care	IG1 and IG2 reduced number of falls compared with CG.
Suttanon et al. 2013, Australia	N=40 Mean age 81.9 years Female 63% Mean MMSE 21.3	IG: HE, total of 6 home visits by physiotherapist and 5 follow-up phone calls in 6 months + self-training 5/wk, 6 months CG: education re. dementia and aging in total of 6 home-visits by occupational therapist and 5 follow-up phone calls in 6 months	Follow-up 6 months. IG improved significantly in two physical function test scores compared with the controls. A trend towards reduced falls and number of fallers in the IG compared with CG but no significant difference.

Table 4. Continued…

Study, country	Participants	Intervention	Results
Wesson et al. 2013, Australia	N=22 Mean age 79.8 years Female 41% Mean MMSE 23.5	IG: HE, 6 occupational therapy home visits (and 3 phone calls), 5 home visits by a physiotherapist. Participants were asked to exercise 3 times/wk. CG: usual care.	Follow-up 4 months. No significant difference in the risk of falling or number of falls.
Zieschang et al. 2017, Germany	N=110 Mean age 82.2 years Female 74% Mean MMSE 22	IG: GE, resistance training, 120 min, 2/wk, 3 months CG: placebo motor training in group (for example flexibility), 60 min, 2/wk, 3 months	IG: reduced number of falls *vs.* CG in the subgroup of multiple fallers during 12 months of follow-up.

AD=Alzheimer Disease; ADL=Activities of Daily Living; CG=Control Group; Fried=Fried frailty criteria (Fried et al. 2001); GE=Group Exercise; HE=Home exercise; IG=Intervention Group; IU=International Unit; MMSE=Mini-Mental State Examination (Folstein et al. 1975); RCT=Randomized Controlled Trial; Winograd=Winograd's frailty scale (Winograd et al. 1991)

2.3 EXERCISE INTERVENTIONS AMONG OLDER PEOPLE

Lack of exercise is often a major cause of chronic diseases (Booth et al. 2012), and exercise interventions have been used to prevent and treat various diseases and conditions (Pedersen & Saltin 2015). The diversity of exercise interventions in respect of their duration, intensity, and training methods is overwhelming (Gillespie et al. 2012). The interventions have often lasted from three to 12 months, and the weekly training times have also varied (Gillespie et al. 2012). Some studies have concerned only one specific exercise training method such as endurance, strength, tai chi, or balance training, whereas others have involved different combinations of methods (Chin A Paw et al. 2008, Theou et al. 2011, Chou et al. 2012, Gillespie et al. 2012).

2.3.1 EXERCISE INTERVENTIONS IN FRAILTY

Exercise has been investigated among frail persons (Chin A Paw et al. 2008, Theou et al. 2011, Chou et al. 2012). Of different interventions, exercise has shown the most benefit for frail persons by improving their balance, gait speed and functioning (Chin A Paw et al. 2008, Theou et al. 2011, Chou et al. 2012). Various exercise methods have been investigated (Chou et al. 2012). Intensive, long-term and diverse exercise interventions are of most benefit (Theou et al. 2011). Diverse endurance, strength, and balance training seems most effective in reducing the number of falls and in enhancing gait and physical ability to function among physically frail older persons (Cadore et al. 2013b). Multicomponent interventions including exercise and nutrition have also shown benefits in frailty in respect of physical functioning (Chan et al. 2012, Kim et al. 2015). However, there was no statistically significant additive effect of nutritional supplementation with exercise (Kim et al. 2015).

Some researchers have suggested that prefrail persons may benefit more from exercise intervention than frail persons (Faber et al. 2006). However, another study showed that frail participants benefited the most from physical activity intervention (Cesari et al. 2015). Other researchers have argued that physical activity intervention could even reduce the stage of frailty (Cameron et al. 2013, Cesari et al. 2015).

Table 5 presents previous exercise interventions in frailty.

Table 5. Exercise trials to intervene or prevent frailty.

Study, country	Participants	Frailty criteria	Intervention	Outcomes
Exercise interventions				
Lustosa et al. 2011, Brazil	N=48 Mean age 72.0 Females 100% Community-dwelling prefrail people	Fried	IG: GE, 60 min, 3/wk, 10 wk CG: No activity	IG showed improvement in physical functioning
Langlois et al. 2013, Canada	N=72 Mean Age 72.3 Females 78% Community-dwelling	Fried, FI, modified PPT	IG: GE, 60 min, 3/wk, 12 wk CG: No activity	IG showed significant improvement in physical capacity, cognitive performance, and QoL compared with CG
Cesari et al. 2015, USA	N=424 Mean age 76.8 Females 69% Community-dwelling	Fried	IG: GE, 40–60 min, 2–3/wk, 12 months CG: Educational program	IG showed significantly lower frailty prevalence at 12 months than CG
Tarazona-Santabalbina et al. 2016, Spain	N=100 Mean Age 80.0 Females 54% Community-dwelling	Fried, EFS	IG: GE, 65 min, 5/wk, 24 wk CG: No activity	IG showed reverse in frailty and improvement in physical functioning and cognition, and emotional and social networking

Table 5. Continued…

Study, country	Participants	Frailty criteria	Intervention	Outcomes
Multicomponent interventions including exercise				
Chan et al. 2012, Taiwan	N=117 Mean age 71.4 Females 59% Community-dwelling	Modified Fried	IG1, EN: 60 min, 3/wk, 3 months + nutritional advice IG2, PST: 6 sessions during 3 months on solving "here-and-now" problems CG: usual care Educational booklet to IG1, IG2, and CG Follow-up 12 months	IG1 improved in frailty status in 3 months, but improvement did not last for 6 or 12 months compared with CG.
Fairhall et al. 2012, Australia	N=241 Mean age 83.3 Females 68% Community-dwelling	Modified Fried	IG: HE 45–60 min, total of 5 times in months 1–3 and 5 times in months 4–12, dietary and psychological care, follow-up 12 months CG: Usual community care	IG: Gait speed ↑, activity ↑
Kim et al. 2015, Japan	N=131 Mean age 80.9 Females 100% Community-dwelling	Fried	IG1: EN, 60 min, 2/wk, 12 wk + MFGM nutrition supplement IG2: EP, 60 min, 2/wk, 12 wk + placebo nutrition supplement IG3: N, MFGM nutrition supplement CG: placebo nutrition supplement Follow-up 7 months	IG1 (EN) and IG2 (EP) improved frailty status

CG=Control Group; EFS= Edmonton Frail Scale (Rolfson et al. 2006); EN=Exercise and Nutrition; EP=Exercise + Placebo; FI=Frailty Index (Mitnitski et al. 2001); Fried=Fried frailty criteria (Fried et al. 2001); GE=Group Exercise; HE=Home exercise; IG=Intervention group; MFGM=Milk Fat Globule Membrane; N=Nutrition; PPT=Physical Performance Test (Binder et al. 2004); PST=Problem Solving Therapy; QoL=Quality of Life

2.3.2 EXERCISE INTERVENTIONS TO REDUCE FALLS

Exercise interventions have been widely studied in fall prevention and their diversity is high (Gillespie et al. 2012). Some studies have concerned a single method such as tai chi (Lomas-Vega et al. 2017) whereas others have involved various methods in different combinations (Toulotte et al. 2003). There are also studies on combinations of exercise and other methods (Gillespie et al. 2012). Exercise interventions have included personal training (Suttanon et al. 2013) and group training (Faber et al. 2006), and the intensity has varied (Gillespie et al. 2012).

The most effective exercise interventions in reducing falls have been those combining different exercise methods (Gillespie et al. 2012). The characteristics of participants also affect the outcomes of exercise interventions (Faber et al. 2006). For example, a moderate-intensity exercise program had positive effects on falling in prefrail persons but not in frail persons (Faber et al. 2006). Exercise interventions to prevent falls are also presented above (Section 2.2.5 Prevention of falls and Table 4 in the same section).

2.3.3 EXERCISE INTERVENTIONS IN DEMENTIA

A meta-analysis revealed that physical exercise training has the potential to reduce the number of falls among persons with dementia or cognitive impairment (Chan et al. 2015). A few exercise studies among persons with dementia have been performed among community-dwelling people (Pitkala et al. 2010). The Finnish Alzheimer disease exercise trial (FINALEX) showed that intensive and long-term exercise training benefits the physical functioning of persons with AD and it also reduced the number of falls without increasing the costs of health and social services and without causing serious adverse effects (Pitkala et al. 2013). Exercise intervention has benefits for persons with mild or advanced AD (Ohman et al. 2016). Recent systematic reviews and meta-analyses have revealed that physical exercise may significantly prevent falls even among older persons with dementia (Burton et al. 2015) or cognitive impairment (Chan et al. 2015). Exercise may also improve ADL (Lam et al. 2018). (See also Table 4 in Section 2.2.5, Prevention of falls.)

2.4 SUMMARY OF THE LITERATURE

There is no international consensus on the definition of frailty (Fulop et al. 2010, Azzopardi et al. 2016), and its prevalence varies according to the various frailty measures (Fried et al. 2001, Song et al. 2010, Jurschik et al. 2012, Malmstrom et al. 2014, Kojima et al. 2015, Widagdo et al. 2015). However, there is a scarcity of studies on comparison of various frailty measures in a single population. Frailty indicates a poor prognosis irrespective of the measure used (Woo et al. 2012). Postal questionnaire-based frailty measures have provided a simple way to investigate frailty (Sirola et al. 2011).

Dementia and frailty have mutual risk factors (Sampson 2012) and the syndromes often overlap (Robertson et al. 2013). Both persons with frailty or with dementia are known to benefit from exercise interventions (Chan et al. 2015, de Labra et al. 2015). However, it is not known whether the stage of frailty affects the benefits of exercise intervention in respect of physical functioning among persons with dementia.

Factors behind falls have been widely studied in the general population (AGS 2011). A number of risk factors of falls have been identified, such as a history of falls, poor physical functioning, FRDs, and certain diseases (Tinetti et al. 1988, Campbell et al. 1999, Leipzig et al. 1999, AGS 2001, Stalenhoef et al. 2002, AGS 2011). However, there are fewer studies on risk factors and especially on circumstances of falls among persons with dementia (AGS 2011).

It is known FRDs such as psychotropics, DAPs, and antihypertensives increase fall risk in the general older population (Hartikainen et al. 2007, Woolcott et al. 2009, Cardwell et al. 2015, Mayer et al. 2017). Exercise has the potential to reduce fall risk among both older people in general (Gillespie et al. 2012) as well as among persons with cognitive impairment (Chan et al. 2015). To my knowledge, there have been no studies on possible interactions between FRDs and exercise interventions.

3 AIMS OF THE STUDY

These studies concern the prognostic significance of frailty measures and they explore exercise effects and their interaction with frailty and fall-related drugs among people with dementia.

Specific aims were as follows:

1. To explore the overlapping of three different frailty measures (HBS, modified WHI-OS, FI) in identifying frail individuals among older men (Study I)
2. To explore how different frailty stages according to three frailty measures are associated with falls, weight change, QoL, and mortality during a five-year follow-up period (Study I)
3. To explore how the severity of a frailty stage affects the benefits of exercise intervention among people with AD in respect of physical functioning and falls (Study II)
4. To explore features of falls among people with AD (Study III)
5. To identify possible risk factors of falls among people with AD (Study III)
6. To explore possible interactions between exercise intervention and fall-related drugs on fall risk among people with AD (Study IV)

4 METHODS

4.1 PARTICIPANTS

4.1.1 PARTICIPANTS IN THE HELSINKI BUSINESSMEN STUDY

The Finnish Institute of Occupational Health organized health check-ups in the 1960s and 1970s to diminish cardiovascular risk among Finnish upper-social-class businessmen. The participants (N=3490) were all men who had been born in 1919–1934 and had worked as executives or businessmen. They received health education and their risk factors were evaluated by means of laboratory and clinical examinations and questionnaires in 1964–1973.

Of the men showing an interest in participating in a five-year prevention trial (starting in 1974) 1604 were clinically healthy but had a high risk of cardiovascular disease (CVD). The rest (N=1886) were sick, dead, refused, did not respond to the postal questionnaire or had no risk factors. Those healthy men at a high risk of CVD were randomized into intervention (N=612) and control (N=610) groups. A low-risk control group (N=593) was formed of those not having risk factors for CVD. The formed groups participated in a 5-year multifactorial prevention trial in 1974–1980. Examinations ten years post-trial revealed no benefit in terms of coronary heart disease or mortality. Later, the emphasis shifted from the prevention of CVD to geriatric medicine. Follow-up has been conducted by means of postal questionnaires since 2000.

In 2000, a postal questionnaire was sent to survivors of the Helsinki Businessmen Study cohort (N=1390) and the majority (N=996, 72%) responded. In 2005, a postal questionnaire was sent to a random subcohort (N=996). Of these men, 742 responded and 480 had all the needed information for analyses available. The year 2000 questionnaire data was used as baseline data and all participants that had all information available concerning frailty measures and follow-up data (until 2005) were included (N=480). Those with missing items and those not included in the subcohort (N=516) did not differ from those responding to frailty measures as regards age, comorbidities, or baseline distribution of frailty measures (HBS, modified WHI-OS, FI). Figure 3 shows the flowchart of the Helsinki Businessmen Study.

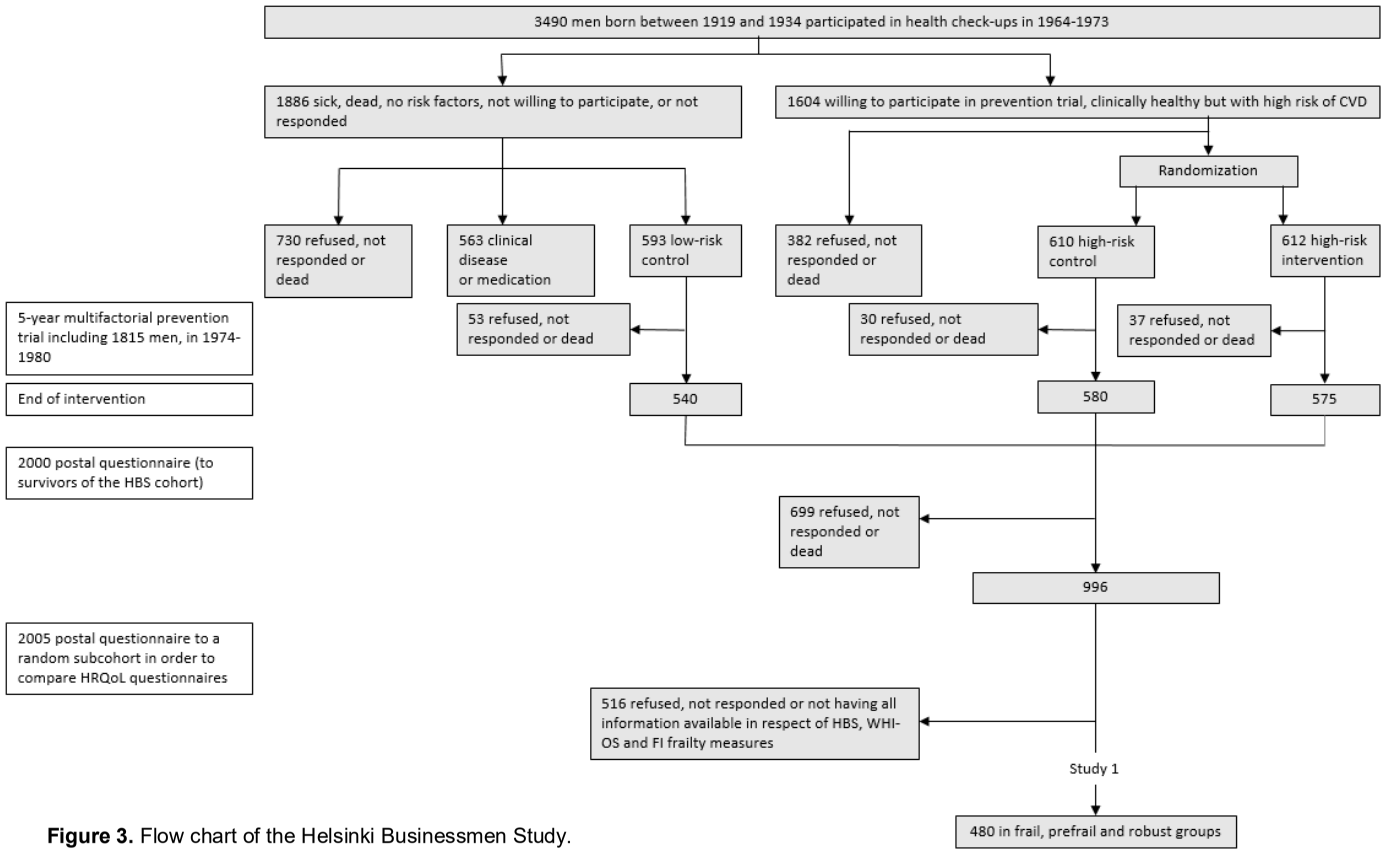

Figure 3. Flow chart of the Helsinki Businessmen Study.

4.1.2 PARTICIPANTS IN THE FINALEX STUDY

In 2008, the AD drug reimbursement register of the Social Insurance Institution of Finland was used to identify persons with AD living with a spouse in Helsinki, Espoo or Vantaa (N=1264). They were mailed a letter offering the possibility to participate in an exercise trial. Of those sending back a prepaid response letter and expressing interest in participating (N=497), study nurses managed to contact 390 persons by telephone. Of these, 84 declined participation and 96 did not fulfil the inclusion criteria.

The inclusion criteria were investigated by study nurses by telephone and were as follows:

- Finnish-speaking
- living with a spouse at home
- living in Helsinki, Espoo or Vantaa
- age ≥65 years, retired
- no diagnosed terminal disease or severe hemiplegia
- ability to walk independently with or without a mobility aid
- having at least one of the following signs of possible frailty: unintentional weight loss, or decreased walking speed, or ≥1 fall during the previous year

A total of 210 participants fulfilled the inclusion criteria and were included in the FINALEX study. These participant-caregiver dyads were randomized in blocks of 30 between April 28, 2008 and August 8, 2009. Computer-generated randomly allocated numbers received from a randomization center by telephone were used to perform the randomization. The identities of the potential participants were not known in the randomization center. A study nurse called the randomization center and read the names in the order they were on a printed list. The 210 participants were randomized into three groups each consisting of 70 dyads: home-based intervention group, group-based intervention group, and control group. Five participants died and eleven declined to participate immediately after randomization, resulting in 194 participants in these analyses. The final numbers of participants in the FINALEX study were: home-based intervention group (N=68), group-based intervention group (N=61) and control group (N=65). Both intervention groups exercised for approximately one hour twice a week for one year, with similar training methods. In the present analyses the two intervention groups were merged into a single intervention group (N=129). The control group was the same as in the original FINALEX study. Figure 4 shows the flowchart of the FINALEX study.

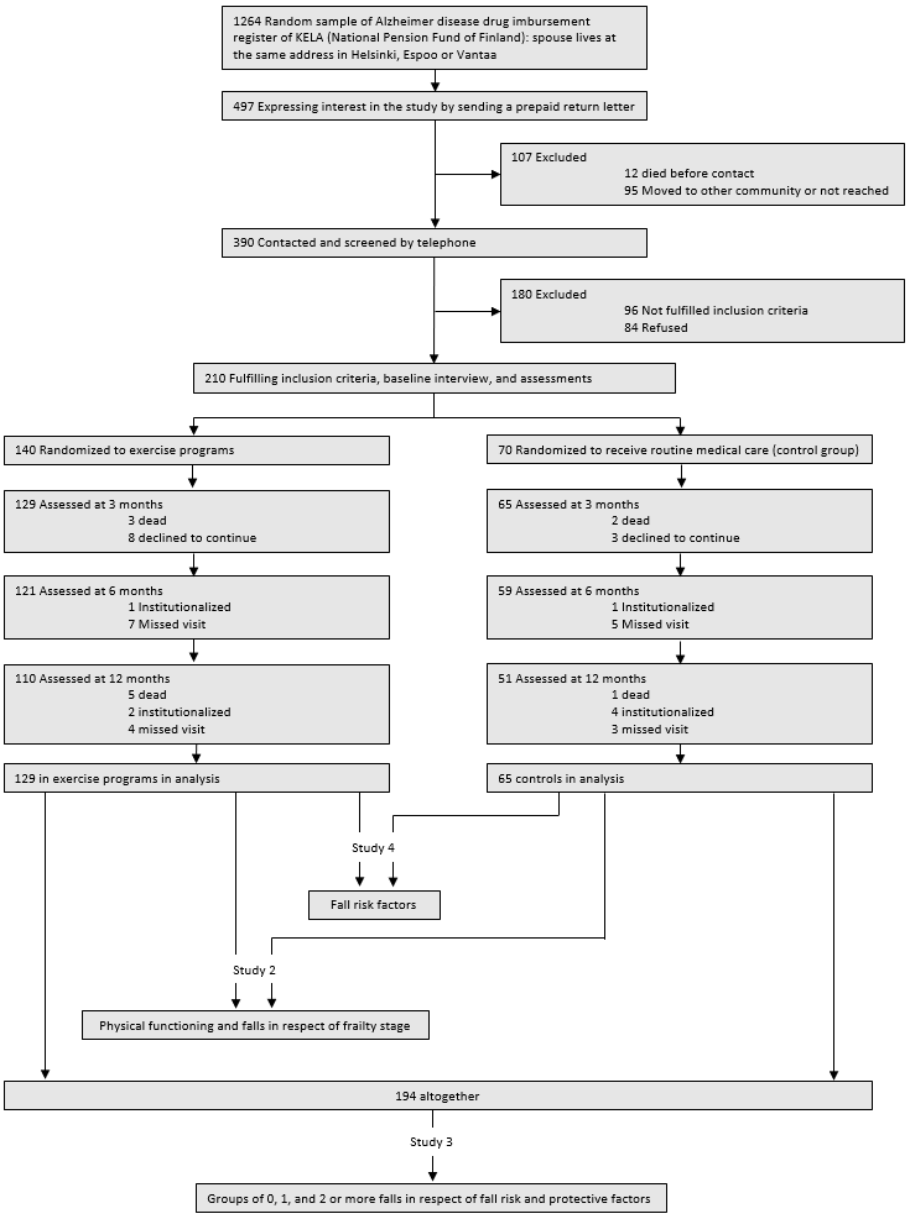

Figure 4. Flow chart of the FINALEX study.

Table 6 shows baseline characteristics of the participants in the Helsinki Businessmen Study and in the FINALEX study.

Table 6. Baseline characteristics of the participants in the Helsinki Businessmen Study and in the FINALEX study.

	Helsinki Businessmen Study	FINALEX study	
		Intervention groups	Control group
	N=480	N=129	N=65
Age, mean (SD)	73 (4)	78 (5)	78 (5)
Male, n (%)	480 (100)	80 (62)	39 (60)
Married, n (%)	424 (88)	129 (100)	65 (100)
Education <8 y, n (%)	0 (0)	48 (37)	29 (45)
Charlson, mean (SD)	1.3 (1.4)	2.6 (1.8)	3.0 (1.7)
Charlson=Charlson comorbidity index (Charlson et al. 1987); SD=Standard deviation			

4.2 ASSESSMENT METHODS

4.2.1 ASSESSMENT METHODS IN THE HELSINKI BUSINESSMEN STUDY

The included analyses of the Helsinki Businessmen Study are based on the postal questionnaires in 2000 and 2005 (both are shown in the appendices). In both years, the postal questionnaires were sent to the participants and they included a prepaid response letter. The participants completed the postal questionnaires themselves or in few cases with the help of relatives when needed.

The postal questionnaires included details on demographics such as age, marital status, weight (kg), and BMI (kg/m^2). Diseases (yes/no) were inquired about and confirmed in the register of the Social Insurance Institution of Finland. The Charlson comorbidity index was constructed as described (Charlson et al. 1987). Physical activity including exercise hours per week, current smoking status, and alcohol consumption behavior (type and amount) were inquired about.

The 2000 questionnaire also included the RAND-36 (Hays & Morales 2001). The RAND-36 instrument assesses individuals' health-related quality of life (HRQoL) (Hays & Morales 2001). It consists of 36 items assessing eight health domains: physical functioning (ten items), role limitations caused by physical health problems (four items), role limitations caused by emotional problems (three items), social functioning (two items), emotional well-being (five items), energy/fatigue (four items), pain (two items), and general health perceptions (five items) (Hays & Morales 2001). A change in perceived health during the previous year is assessed via an additional single item (Hays & Morales 2001). Each item scores between 0 and 100, and then averages for each domain are calculated (Hays & Morales 2001). Validation has been investigated in several studies over the years (Samsa et al. 1999). A difference

of 3 to 5 points in a domain is suggested to be clinically important (Samsa et al. 1999). In this study RAND-36 was used in construction of frailty measures. In addition, weight change data from 1974 to 2000 were retrieved from the 1974 and 2000 questionnaire data. The 2005 questionnaire contained a question on falls during the past year (yes, several times per year/yes, 1 or 2 times per year/no). A participant was defined as a faller if they had fallen at least once during the past year. Weight change from 2000 to 2005 was calculated on the basis of answers in the questionnaires.

The 15D HRQoL instrument was embedded in the 2005 questionnaire. The 15D instrument assesses the HRQoL of the patients (Sintonen 2001). It is a comprehensive and generic instrument used to measure adults' HRQoL. There are 15 dimensions in the 15D: hearing, vision, breathing, eating, sleeping, speech, mobility, usual activities, mental function, discomfort and symptoms, distress, depression, vitality, elimination, and sexual activity. The 15D score is generated by using a set of utility or preference weights, and the index scores are between 0 (lowest HRQoL) and 1 (highest HRQoL). The 15D is well comparable with other preference-based generic instruments (Hawthorne et al. 2001, Stavem et al. 2005). There has been systematic validation for the 15D since the 1970s in different population samples. Development has progressed according to the feedback of both patients and experts. The 15D is normally filled in by the subject but it can also be filled in via an interview with the subject or their proxy. A difference of 0.02 to 0.03 in the 15D score between patient groups has been considered clinically significant (Sintonen 2001).

Mortality data were retrieved from the Population Information System maintaining a register of all Finnish citizens, thus giving 100% coverage.

The two phenotypic frailty measures HBS (Sirola et al. 2011) and WHI-OS (Woods et al. 2005) are based on Fried criteria (Fried et al. 2001). The FI measure includes physical, psychological, cognitive, and social dimensions (Mitnitski et al. 2001, Fisher 2005). The number and extent of the dimensions included have varied between studies (Song et al. 2010). The FI was calculated as the number of conditions present divided by the number of items measured, which was 20 in Study I. Cut-off scores of ≥0.25 for frail, 0.08–0.249 for prefrail and <0.08 for not frail were used, as they have been used earlier (Song et al. 2010). Table 7 summarizes the three frailty measures examined in Study I.

Table 7. Construction of frailty measures (Helsinki Businessmen Study [HBS], modified Women's Health Initiative Observational Study [WHI-OS], Frailty Index [FI]) for Study I. RAND-36=RAND-36 measure (Hays & Morales 2001)

HBS (Sirola et al. 2011)	**Modified WHI-OS** (Woods et al. 2005)	**Frailty Index** (Mitnitski et al. 2001)
Weakness, 1 p difficulty in lifting or carrying a grocery bag, self-reported from RAND-36	**Weakness/slowness, 2 p** RAND-36 Physical Function scale: score <75	**Diseases: each assessed as present (1 p) or not present (0 p):** coronary heart disease, heart failure, atherosclerosis, hypertension, diabetes, chronic pulmonary disease, musculoskeletal disease, mental health disturbance, memory disturbance, cerebrovascular disorder, cancer, other disease
Exhaustion, 1 p low energy all or most of the time in the last 4 weeks, self-reported (from RAND-36: a question in the Vitality Scale)	**Exhaustion, 1 p** RAND-36 Vitality Scale over past 4 weeks: "Did you feel worn out? Did you feel tired? Did you have a lot of energy? Did you feel full of pep?": score <55	**Features: the next five features from RAND-36 were investigated and the lowest 10% percentile was assessed as each feature present (1 p):** general health, vitality, subjective mental health, physical functioning, bodily pain
Physical inactivity, 1 p answering "no" to question "do you exercise regularly weekly?"	**Physical inactivity, 1 p** answering "no" to question "do you exercise regularly weekly?"	
Unintentional weight loss, 1 p Body Mass Index (BMI) <21 kg/m² in 2000 or >5% from 1974 to 2000	**Unintentional weight loss, 1 p** Body Mass Index (BMI) <21 kg/m² in 2000 or >5% from 1974 to 2000	**Other: each assessed as present (1 p) or not present (0 p):** institutionalization, being in a hospital during the last five years, and lowered functioning (self-estimated)
Frailty measure: 0 point: not frail 1-2 points: prefrail 3-4 points: frail	**Frailty measure:** 0 point: not frail 1-2 points: prefrail 3-5 points: frail	**Frailty measure:** Frailty Index was defined as the number of conditions present divided by total number, 20, of features assessed: <0.08 not frail; 0.08–0.249: prefrail; ≥0.25: frail

4.2.2 ASSESSMENT METHODS IN THE FINALEX STUDY

Those spousal dyads fulfilling the inclusion criteria (N=210) were invited to an appointment with study nurses. They were given written and oral information about the study and they gave their written informed consent. The spouses gave consent for the participants with reduced judgement capacity (Clinical Dementia Rating [CDR] scale >1). One study nurse interviewed the patient while another study nurse interviewed the spouse at the same time.

All participants were evaluated by the study nurses at baseline and at three, six, and 12 months.

Demographic factors (age, sex, education) were collected from the participants. They were assessed on their mobility and physical functioning as well as cognitive functioning. Diseases of the participants and types of medication were enquired about and they were verified from the medical records brought by the dyads. The Charlson comorbidity index was calculated (Charlson et al. 1987). This index gives a measure of the load and prognosis of comorbidities (Charlson et al. 1987). Participants' height, weight and blood pressure were measured.

The Mini Nutritional Assessment (MNA) measure served to assess the nutritional status of the participants (Guigoz et al. 2002, Guigoz 2006). The MNA consists of 18 questions (six for screening and twelve for assessment). For each question the lowest score is 0 and the highest score ranges from 1 to 3. Total points come to 0 to 30, of which points <17 indicate malnutrition, points from 17 to 23.5 indicate risk of malnutrition, and points from 24 to 30 indicate normal nutritional status. The MNA measure is shown in the appendices.

The Functional Independence Measure (FIM) (Pollak et al. 1996) served to assess both physical and cognitive functioning. It was used at baseline and at three, six, and 12 months. The FIM consists of 18 categories of which five concern cognitive functioning and 13 concern physical functioning. Each category is rated on a scale from 1 to 7, in which 1 refers to total assistance required and 7 refers to full independence. The total score ranges from 18 to 126 points. The lower the score, the more likely the person needs assistance (Pollak et al. 1996).

A modified Short Physical Performance Battery (SPPB) (Guralnik et al. 1994) served to evaluate the physical functioning of the participants. The SPPB measures physical functioning of the lower extremities and consists of three parts: 1) gait speed is measured over a distance of 2.4 meters which the person is asked to walk at their natural speed (in FINALEX the distance used was 10 meters instead), 2) total time to rise from a chair and return to a seated position five times is measured (in FINALEX three times instead), and 3) balance is evaluated by examining the ability to stand with the feet together in side-by-side, semi-tandem, and tandem positions for a maximum of 10

seconds each (in FINALEX the maximum time was 15 seconds). The SPPB was evaluated as described (Guralnik et al. 1994) and is shown in the appendices.

The Timed Up & Go test (Podsiadlo & Richardson 1991) also served to evaluate physical functioning. The test measures objectively the time in which the person rises from a chair, walks three meters, turns, walks back, and sits down again. Groups of <20 seconds, 20–29 seconds, and 30 seconds or more have been used (Podsiadlo & Richardson 1991). The time score correlates with balance and gait speed (Podsiadlo & Richardson 1991). The present study shows the scores in relation to incidence rate ratios (IRRs) of falls per 1-standard deviation (1-SD).

The participants' cognitive status was evaluated by MMSE (Folstein et al. 1975) and CDR (Hughes et al. 1982). MMSE evaluates orientation to time and place, registration, attention and calculation, recall, naming, repetition, and complex command. The total score ranges from 0 to 30, of which 0–11 points refer to severe dementia, 12–17 refer to moderate dementia, 18–23 refer to mild dementia/cognitive impairment, and 24–30 refer to normal cognitive functioning. The MMSE is shown in the appendices.

CDR evaluates the stage of cognitive disorder and dementia and is based on interviews of the patient and his/her proxy, and clinical assessment. CDR consists of six parts: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Each part scores 0 (no impairment), 0.5 (questionable impairment; not in personal care category), 1 (mild impairment), 2 (moderate impairment), or 3 points (severe impairment). The memory part defines the CDR stage. Other parts may shift the stage defined by the memory part by one level to a more severe or a milder stage. The CDR scores for dementia are as follows: 0 none, 0.5 very mild cognitive decline (possible dementia), 1 mild, 2 moderate, and 3 severe (Hughes et al. 1982).

The Cornell Scale for Depression in Dementia was used to evaluate symptoms of depression (Alexopoulos et al. 1988). The scale consists of 19 items including questions about mood-related signs, behavioral disturbances, physical signs, cyclic functions, and ideational disturbances. Evaluation is based on interviews of both patient and spouse or nursing staff member. All items are evaluated as either 0=absent, 1=mild or intermittent, or 2=severe. The total score ranges from 0 to 38, in which lower scores refer to no depression or mild depression symptoms and scores of 13 and higher refer to more severe depression (Alexopoulos et al. 1988).

In Study II, the frailty measure was phenotype-based and consisted of five criteria: 1) unintentional weight loss was asked about from the spouse (yes/no), 2) exhaustion was based on the "lack of energy" item in the Cornell Scale for Depression (gets exhausted easily, is not able to sustain activity) (Alexopoulos et al. 1988), 3) low physical activity was based on the question "do you have an exercise hobby" (yes/no), 4) slow gait speed was defined as <0.85 m/s and measured in the SPPB test (Guralnik et al. 1994), and 5) weakness was based on grip strength measured and adjusted for BMI (≤17 kg,

if BMI ≤23 kg/m²; ≤17.3 kg, if BMI 23–26 kg/m²; ≤18 kg, if BMI 26–29 kg/m²; ≤21 kg, if BMI ≥29 kg/m²). As all participants had to have at least one of the signs of possible frailty (decreased walking speed, ≥1 fall during the previous 12 months, or unintentional weight loss), they were classified into either prefrail intervention (PRI) or prefrail control (PRC) groups (0 or 1 of the five criteria) or into advanced frailty intervention (AFI) and advanced frailty control (AFC) groups (2–5 of the five criteria).

In baseline assessment, the spouses were asked about the participants' possible falls in the previous year. Falls during the follow-up period of the study (12 months) were based on fall diaries kept by the spouses.

Polypharmacy was defined as regularly taking ≥9 forms of systemic medication. Antihypertensives included medications with the Anatomical Therapeutic Chemical classification system of the World Health Organization (WHO ATC) codes (WHO 2017) C03 (diuretics), C07 (beta-blocking agents), C08 (calcium channel blockers) and C09 (agents acting on the renin-angiotensin system). Psychotropics included medications with the WHO ATC codes N05A (antipsychotics), N05B (anxiolytics), N05C (hypnotics and sedatives) and N06A (antidepressants). Opioids included medications with the WHO ATC codes N02A (opioids). DAPs were defined according to the Anticholinergic Risk Scale (Rudolph et al. 2008) and B01AC07 (dipyridamole), R05DA04 (codeine) and N02AX02 (tramadol) from the Anticholinergic Drug Scale (Carnahan et al. 2006) were also included.

4.3 INTERVENTION IN THE FINALEX STUDY

The FINALEX study consisted of two intervention arms: the home-based intervention group and the group-based intervention group. The home-based intervention group exercised one hour twice a week for one year at home. A physiotherapist supervised all training sessions. The group-based intervention group also exercised twice a week for one year. The sessions were held at daycare centers to which the participants were transported by taxis. Two physiotherapists supervised the sessions of ten participants. The visits to daycare centers lasted four hours (including lunch), of which individual training time was approximately one hour.

The spouses of the participants in both intervention groups cooperated in the study and a few more intensive rehabilitation periods in institutional settings were organized if needed. Both intervention groups were assessed by a geriatrician and a plan for rehabilitation was drawn up. The geriatrician's assessment ensured safety of the intervention. Home-based exercise training was tailored according to the participant's needs, whereas the group-based intervention group exercised according to a preplanned exercise program consisting of strength, balance, multitasking, aerobic and endurance training. The intervention involved individually increasing weights during the study

period. The control group received normal community care; physiotherapy was also allowed.

Study nurses assessed all groups at baseline, and at three, six and 12 months. All groups were given information about AD, the symptoms and consequences of the disease, the possibilities of treatment and rehabilitation, and written advice on exercise, nutrition and vitamin D. Table 8 summarizes exercise intervention methods in the home-based and group-based exercise intervention groups.

Table 8. Methods in home-based and group-based intervention in the FINALEX study.

Component of training	Home-Based Exercise	Group Exercise
Aerobic	Pedal exerciser, exercise bike, Nordic walking outdoors	Pedal exerciser, rowing machine, dancing, Nordic walking outdoors
Strength	Training with ankle and hand weights	Training with various equipment in the gym
Balance	Training with balance pillows, climbing stairs, picking up items from floor, rising from floor	Trampoline jumping, walking on balance line or beam, picking up items from floor level, climbing a ladder, bouncing a ball, rising from floor
Executive functioning	Throwing a ball accurately, dual-tasking (e.g. singing while training, performing different functions with right and left hands while counting backward)	Throwing a ball accurately, dual-tasking (e.g. singing while training, performing different functions with right and left hands while counting backward)

4.4 STATISTICAL ANALYSES

The data are given as means with SDs, as counts and percentages, or as medians with interquartile ranges (IQRs). In Study I the differences between three frailty measures were assessed using generalized linear models with appropriate distribution and link function. Significance tests for estimates of all the models were based on robust standard errors to account for the clustering of participants.

The Cochran–Armitage test and analysis of variance (ANOVA) with orthogonal polynomial contrast were used to test the linearity across the three frailty stages (Study I), and in Study III, when comparing those with none, one or ≥2 falls. In cases of violation of assumptions such as non-normality or when the theoretical distribution of the test statistics was unknown, the boostrap method was used (Studies I and II). The normalities of continuous variables were tested by using Shapiro–Wilk statistics (Studies I, II, III and IV). The *t*-test, the Mann–Whitney *U*-test, the boostrap-type *t*-test or the Chi-square test served to test differences between groups at baseline, as appropriate (Studies II, III, and IV).

Generalized linear mixed-models with unstructured correlation structure were used to analyze repeated measures. Fixed effects were group, time, and group-time interaction (Study II).

The product limit estimate (Kaplan–Meier) of the cumulative "survival" function was used as the basis of time-to-event analysis and the age-adjusted risk of mortality was estimated with the Cox proportional hazard model (Study I). Incidence rates of falls per 1000 person-years with 95% confidence intervals (CIs) were calculated, assuming Poisson distribution. Poisson regression models or negative binomial regression models, when appropriate, were used to calculate adjusted estimates of IRRs for falls (Studies II and III). The Lagrange multiplier test was used to test the assumptions of over-dispersion in the Poisson model (Studies II, III and IV). In Study III the nonlinear relationship between MMSE data and number of drugs *vs.* the incidence of falls was assessed using Poisson regression including quadratic terms. Furthermore, in Study IV Poisson regression models with count of fall events were used to model the relationship between exercise and drugs and these models were adjusted for age, gender, and FIMmotor (motor part of the FIM).

Stata 14.1 and 15.0 statistical packages (StataCorp LP, College Station, TX, USA) were used for the analyses.

4.5 ETHICAL CONSIDERATIONS

The Ethics Committee of Helsinki University Hospital approved the study protocols, and all participants provided informed consent. The Helsinki Businessmen Study began in the 1960s and at that time formalities such as trial registration were rudimentary. The participants of the Helsinki Businessmen Study were told of the design and purpose of the trial; they all gave oral consent and took part voluntarily in the trial. In the FINALEX study spouses provided informed consent for patients with reduced judgment capacity.

5 RESULTS

5.1 CHARACTERISTICS OF PARTICIPANTS IN THE HELSINKI BUSINESSMEN STUDY (STUDY I)

The baseline characteristics of the Helsinki Businessmen Study participants are presented in Table 9. There were 480 participants in the study. Their mean age was 73 years. All Helsinki Businessmen Study participants were male and highly educated. Their mean BMI was slightly over 25 kg/m^2. Their mean Charlson comorbidity index was 1.3.

Table 9. Baseline characteristics in 2000 of frail participants according to the Helsinki Businessmen Study (HBS) measure (Sirola et al. 2011), the modified Women's Health Initiative Observational Study (WHI-OS) measure (Woods et al. 2005), and the Frailty Index (FI) measure (Mitnitski et al. 2001), and characteristics of all participants (ALL).

	HBS frail N=35	WHI-OS frail N=35	FI frail N=86	ALL N=480
Age, mean (SD)	75 (5)	75 (5)	74 (4)	73 (4)
Married, n (%)	31 (89)	30 (86)	76 (88)	424 (88)
Body Mass Index, mean (SD)	24.2 (3.5)	24.0 (3.4)	25.9 (3.4)	25.5 (3.1)
Weight, kg, mean (SD)	77.7 (10.7)	77.9 (11.2)	82.3 (11.5)	81.4 (4.0)
Cancer, n (%)	8 (23)	7 (20)	17 (20)	62 (13)
Cerebrovascular disorder, n (%)	7 (20)	8 (23)	25 (29)	42 (9)
Chronic obstructive pulmonary disease, n (%)	7 (20)	6 (17)	15 (17)	35 (7)
Coronary heart disease, n (%)	9 (26)	10 (29)	33 (38)	79 (16)
Diabetes, n (%)	5 (14)	5 (14)	20 (23)	49 (10)
Heart failure, n (%)	8 (23)	10 (29)	22 (26)	57 (12)
Memory disturbance, n (%)	13 (37)	15 (43)	38 (44)	72 (15)
Musculoskeletal disease, n (%)	17 (49)	17 (49)	44 (51)	116 (24)
Psychiatric illness, n (%)	3 (9)	4 (11)	9 (10)	18 (4)
Charlson, mean (SD)	2.7 (1.8)	2.8 (1.8)	3.0 (1.6)	1.3 (1.4)
Statin user, n (%)	2 (6)	3 (9)	19 (22)	70 (15)
Exercises regularly, n (%)	14 (40)	14 (40)	62 (72)	408 (85)
Exercise hours/week, median (IQR)	0 (0–4)	0 (0–3)	3 (0–6)	5 (3–7)
Smokers, n (%)	5 (14)	6 (17)	8 (9)	38 (8)
Charlson=Charlson comorbidity index (Charlson et al. 1987); IQR= Interquartile range; SD=Standard deviation				

The frail participants according to the HBS frailty measure, the modified WHI-OS frailty measure and the FI frailty measure were old, frequently had diseases such as cancer, cerebrovascular disorder, chronic obstructive pulmonary disease (COPD), heart diseases, memory disturbances and psychiatric illnesses, as well as musculoskeletal diseases, and they exercised for relatively few hours in a week.

5.2 PROGNOSIS OF FRAILTY (STUDY I)

In Study I, the three frailty measures (HBS, WHI-OS, FI) identified partly overlapping but not all the same men as frail. Both HBS and WHI-OS measures identified 35 (7.3%) participants as frail whereas the FI identified 86 (17.9%) as frail. A total of 102 men were identified as frail by at least one frailty measure, and 21 men were identified as frail by all three frailty measures. Figure 5 presents the overlapping of the frail participants according to the three measures at the 2000 baseline in a Venn diagram.

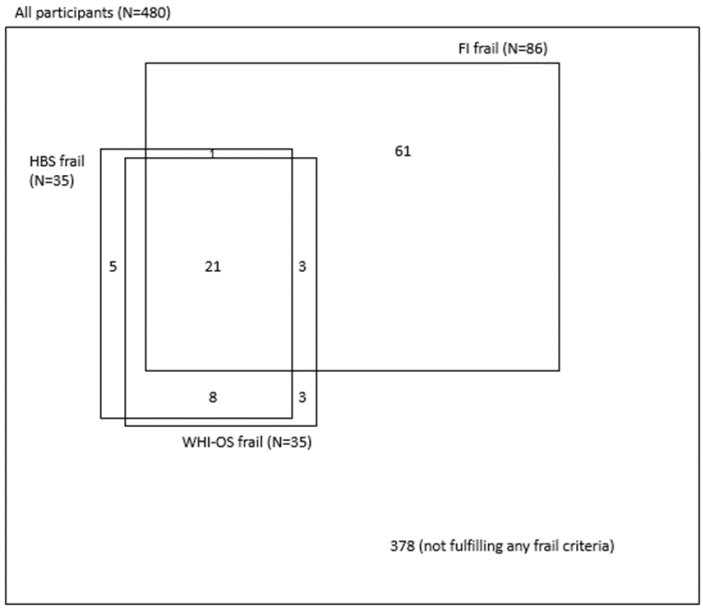

Figure 5. A Venn diagram showing overlapping of the frail participants according to the Helsinki Businessmen Study (HBS) measure (Sirola et al. 2011), the modified Women's Health Initiative Observational Study (WHI-OS) measure (Woods et al. 2005), and the Frailty Index (FI) measure (Mitnitski et al. 2001) at the 2000 baseline.

Fallers in 2005

Figure 6 shows the number of fallers in the year 2000 frailty stage groups according to all three frailty measures. For all three compared measures there were higher proportions of fallers in frail groups than in prefrail or not frail groups in 2005. The difference was significant in all the measures. The proportions of fallers in the HBS groups were 47.1% (N=8) [95% CI: 23.0 to 72.2] in the frail group, 26.4% (N=51) [95% CI: 20.4 to 33.2] in the prefrail group, and 20.7% (N=35) [95% CI: 14.9 to 27.6] in the not frail group (p=0.027). The corresponding values in the WHI-OS groups were 52.9% (N=9) [95% CI: 27.8 to 77.0] in the frail group, 25.8% (N=43) [95% CI: 19.3 to

33.1] in the prefrail group, and 21.5% (N=42) [95% CI: 16.0 to 28.0] in the not frail group (p=0.023). In the FI groups, they were 40.7% (N=22) [95% CI: 27.6 to 55.0] in the frail group, 22.9% (N=35) [95% CI: 16.5 to 30.4] in the prefrail group, and 21.5% (N=37) [95% CI: 15.6 to 28.4] in the not frail group (p=0.016).

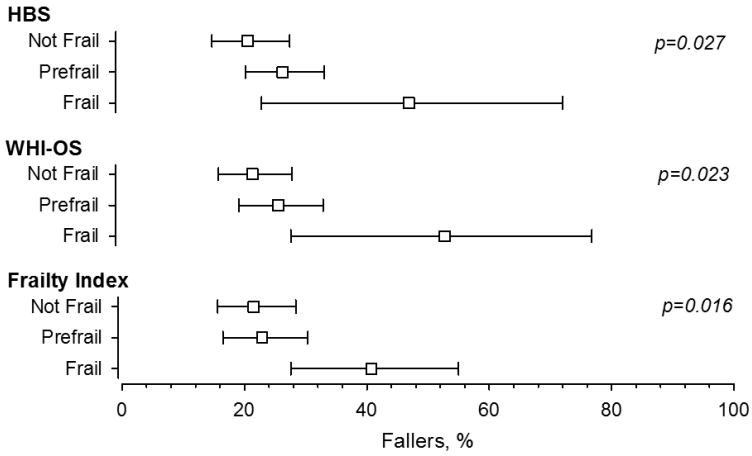

Figure 6. Numbers of fallers in the year 2000 frailty stage groups according to the Helsinki Businessmen Study (HBS) measure (Sirola et al. 2011), the modified Women's Health Initiative Observational Study (WHI-OS) measure (Woods et al. 2005), and the Frailty Index (FI) measure (Mitnitski et al. 2001).

Weight change from 2000 to 2005

Figure 7 shows weight changes from 2000 to 2005. All the groups tended to lose weight, but no significant differences existed between the various frailty groups according to any of the three measures. According to the HBS measure the mean weight change was -0.6 kg [95% CI: -2.6 to 1.4] in the frail group, -1.0 kg [95% CI: -1.5 to -0.4] in the prefrail group, and -0.8 kg [95% CI: -1.4 to -0.1] in the not frail group (p=0.79). The corresponding values as regards the modified WHI-OS measure were -0.5 kg [95% CI: -2.5 to 1.5] in the frail group, -1.0 kg [95 % CI: -1.6 to -0.4] in the prefrail group, and -0.7 kg [95% CI: -1.3 to -0.2] in the not frail group (p=0.69). Regarding the FI, the figures were -1.4 kg [95% CI: -2.5 to -0.3] in the frail group, -0.7 kg [95% CI: -1.3 to -0.0] in the prefrail group, and -0.9 kg [95% CI: -1.4 to -0.3] in the not frail group (p=0.62).

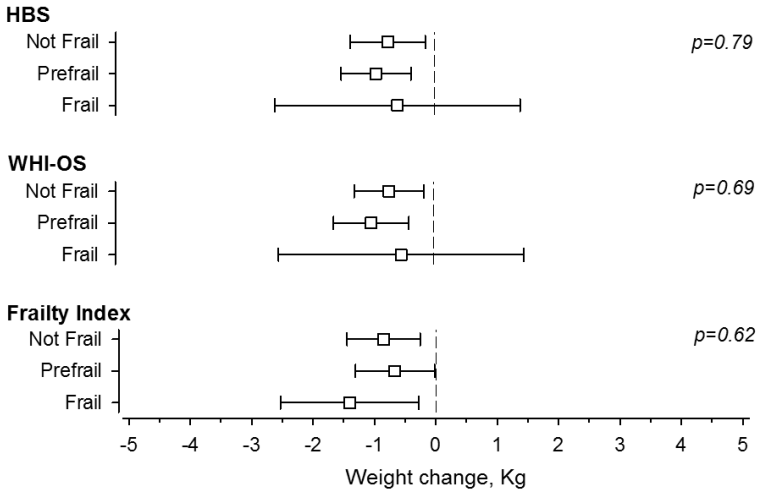

Figure 7. Weight changes from 2000 to 2005 in the year 2000 frailty stage groups according to the Helsinki Businessmen Study (HBS) measure (Sirola et al. 2011), the modified Women's Health Initiative Observational Study (WHI-OS) measure (Woods et al. 2005), and the Frailty Index (FI) measure (Mitnitski et al. 2001).

Quality of life in 2005

Figure 8 shows the QoL in 2005 according to the 15D instrument (Sintonen 2001). With all three measures the HRQoL was found to be lowest in the frail groups. In connection with the HBS measure the mean 15D scores were 0.76 [95% CI: 0.71 to 0.81] in the frail group, 0.87 [95% CI: 0.86 to 0.88] in the prefrail group, and 0.92 [95% CI: 0.91 to 0.93] in the not frail group ($p<0.001$, adjusted for age). The corresponding values as regards the modified WHI-OS measure were 0.74 [95% CI: 0.70 to 0.78] in the frail group, 0.86 [95 % CI: 0.85 to 0.88] in the prefrail group, and 0.92 [95% CI: 0.91 to 0.93] in the not frail group ($p<0.001$, adjusted for age). Regarding the FI, the figures were 0.78 [95% CI: 0.75 to 0.81] in the frail group, 0.88 [95% CI: 0.87 to 0.90] in the prefrail group, and 0.92 [95% CI: 0.92 to 0.93] in the not frail group ($p<0.001$, adjusted for age).

Mortality from 2000 to 2005

Figure 9 shows mortality in different stages of frailty according to the three measures. With all the three measures mortality was greatest in the frail groups. In connection with the HBS measure the mortality rate was 51.4% [95% CI: 36.3 to 68.6] in the frail group, 19.5% [95% CI: 15.1 to 25.0] in the prefrail group, and 8.8% [95% CI: 5.5 to 13.7] in the not frail group ($p<0.001$, adjusted for age). The corresponding values as regards the modified WHI-OS measure were 51.4% [95% CI: 36.3 to 68.6] in the frail group, 21.3% [95% CI: 16.4 to 27.3] in the prefrail group, and 8.5% [95% CI: 5.5 to 13.0] in the not

frail group (p<0.001, adjusted for age). Regarding the FI, the figures were 36.1% [95% CI: 26.9 to 47.1] in the frail group, 19.1% [95% CI: 14.2 to 25.3] in the prefrail group, and 8.0% [95% CI: 5.0 to 12.7] in the not frail group (p<0.001, adjusted for age).

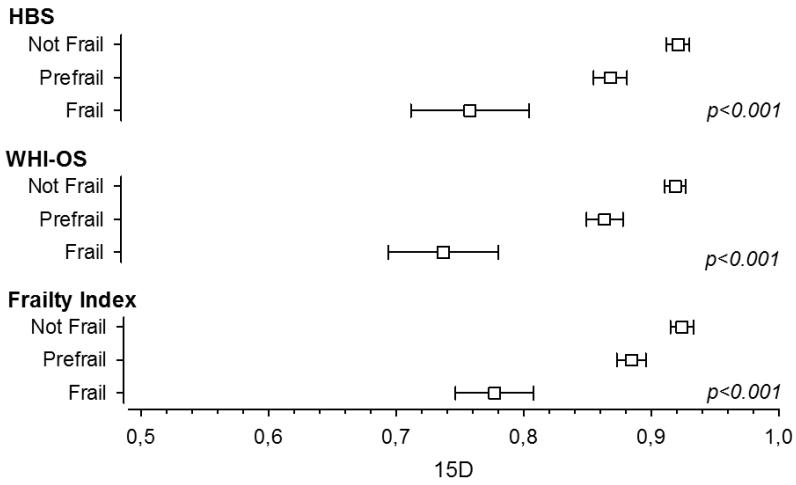

Figure 8. Quality of life (according to the 15D measure (Sintonen 2001)) in 2005 in the year 2000 frailty stage groups according to the Helsinki Businessmen Study (HBS) measure (Sirola et al. 2011), the modified Women's Health Initiative Observational Study (WHI-OS) measure (Woods et al. 2005), and the Frailty Index (FI) measure (Mitnitski et al. 2001).

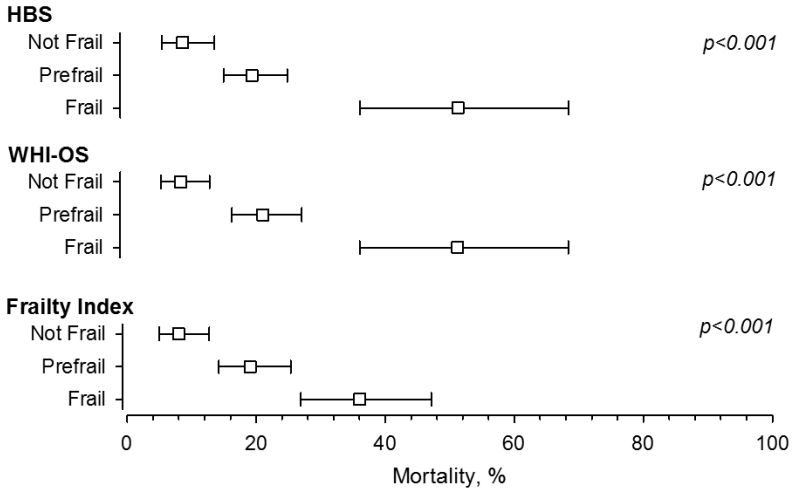

Figure 9. Mortality from 2000 to 2005 in the year 2000 frailty stage groups according to the Helsinki Businessmen Study (HBS) measure (Sirola et al. 2011), the modified Women's Health Initiative Observational Study (WHI-OS) measure (Woods et al. 2005), and the Frailty Index (FI) measure (Mitnitski et al. 2001).

5.3 CHARACTERISTICS OF THE PARTICIPANTS IN THE FINALEX STUDY (STUDIES II, III AND IV)

The baseline characteristics of the 194 FINALEX participants are presented in Table 10. The participants in the intervention and control groups are shown separately. Their mean age was 78 years. Of the participants, three out of five were male. Two in five participants had less than eight years of education. Mean BMI was slightly over 25 kg/m^2. The participants used seven drugs on average and the Charlson comorbidity index was three. There were no significant differences in characteristics between the intervention and control groups.

Table 10. Baseline characteristics in control and intervention groups in the FINALEX study.

	Intervention N=129	Control N=65	p-value*
Men, n (%)	80 (62)	39 (60)	0.79
Age (years), mean (SD)	78 (5)	78 (5)	0.75
Education <8 years, n (%)	48 (37)	29 (45)	0.32
MNA, mean (SD)	23 (2)	22 (2)	0.29
BMI, kg/m^2, mean (SD)	25.9 (3.4)	25.0 (3.9)	0.12
Blood pressure, mean (SD)			
Systolic	150 (25)	150 (27)	0.97
Diastolic	77 (12)	75 (12)	0.22
Number of drugs, mean (SD)	6.5 (3.6)	6.6 (3.0)	0.94
CDR, n (%)			0.72
0.5–1	44 (34)	22 (34)	
2	61 (47)	34 (52)	
3	24 (19)	9 (14)	
Charlson index, mean (SD)	2.6 (1.8)	3.0 (1.7)	0.12
SPPB total, mean (SD)	9.6 (2.3)	9.8 (2.0)	0.23
FIM Total, mean (SD)	88 (19)	88 (18)	0.85
Vision problem, n (%)	9 (7)	8 (12)	0.22
Fallen in previous year, n (%)	48 (37)	32 (49)	0.11

*Differences between groups were tested by *t*-test, bootstrap-type *t*-test or Chi-square test; BMI=body mass index; CDR=Clinical Dementia Rating scale (Hughes et al. 1982); Charlson index=Charlson comorbidity index (Charlson et al. 1987); FIM=Functional Independence Measure (Pollak et al. 1996); MNA=Mini-Nutritional Assessment (Guigoz et al. 2002); SD=standard deviation; SPPB=Short Physical Performance Battery (Guralnik et al. 1994)

5.4 FRAILTY IN MODIFYING THE EFFECTS OF EXERCISE AMONG PEOPLE WITH ALZHEIMER DISEASE (STUDY II)

The participants (129 in the intervention groups and 65 in the control groups) were classified into the prefrail (0–1 criteria present) groups PRI (N=73) and PRC (N=38), and advanced frailty (2–5 criteria present) groups AFI (N=56) and AFC (N=27).

Effects of exercise intervention on physical function

Figure 10, left panel, shows the changes in FIM scores in the prefrail intervention (PRI) and control (PRC) groups during the 12 months of follow-up. FIM scores showed deterioration in both the PRI and PRC groups. However, the rate of decline was slower in the PRI group than in the PRC group. The mean difference between the PRI and PRC groups was significant at 12 months, as the changes in FIM scores were -6.6 [95% CI: -8.6 to -4.5] in the PRI group and -11.1 [95% CI: -13.9 to -8.3] in the PRC group; p=0.010 (adjusted for sex, age and comorbidities).

Figure 10, right panel, shows the changes in FIM scores in the advanced frailty intervention (AFI) and control (AFC) groups during the 12 months of follow-up. FIM scores showed deterioration in both the AFI and AFC groups. However, the rate of decline was slower in the AFI group than in the AFC group. The mean difference between the AFI and AFC groups was significant at six months (FIM score change, -8.1 [95% CI: -11.1 to -5.2] in the AFI group and -15.5 [95% CI: -20.0 to -11.1] in the AFC group; p=0.007 adjusted for age, sex and comorbidities) and at 12 months (FIM score change, -8.9 [95% CI: -11.9 to -5.9] in the AFI group and -15.3 [95% CI: -20.2 to -10.3] in the AFC group; p=0.031 adjusted for sex, age and comorbidities).

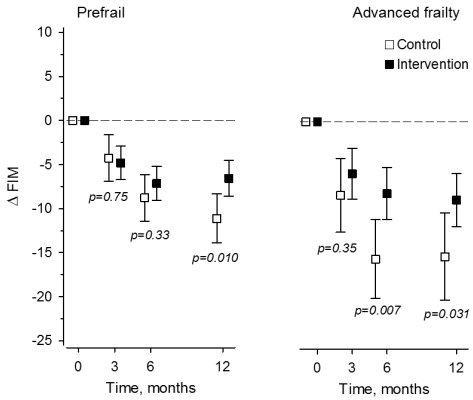

Figure 10. Changes in Functional Independence Measure (FIM) scores (Pollak et al. 1996) in intervention and control groups within the prefrail and advanced-frailty groups.

Effects of exercise intervention on falls

Figure 11 shows the effects of exercise intervention on falls during the 12 months of follow-up. Among prefrail participants (Figure 11, left panel) the PRI group had a significantly lower fall rate (1.14 falls/person-year [95% CI: 0.90 to 1.43]) than the PRC group (1.82 falls/person-year [95% CI: 1.40 to

2.32]). The IRR was 0.63 (95% CI: 0.45 to 0.89; p=0.008, adjusted for age, sex and comorbidities).

Among advanced-frailty participants (Figure 11, right panel) the AFI group had a significantly lower fall rate (2.15 falls/person-year [95% CI: 1.76 to 2.59]) than the AFC group (5.32 falls/person-year [95% CI: 4.36 to 6.44]). The IRR was 0.43 (95% CI: 0.33 to 0.57; p<0.001 adjusted for age, sex and comorbidities).

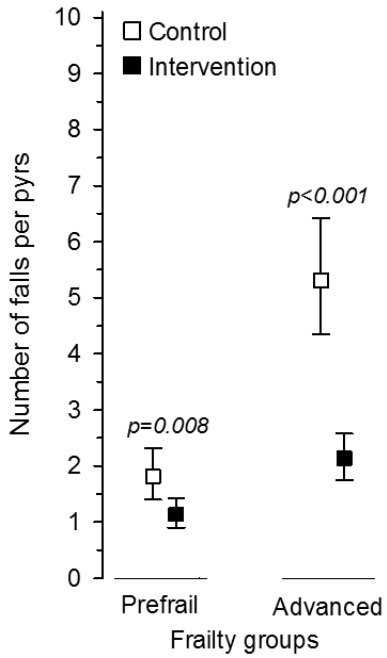

Figure 11. Number of falls per person-years (pyrs) in intervention and control groups within the prefrail and advanced frailty groups during the 12 months of follow-up.

In addition, a novel table (Table 11) shows the numbers of fallers in intervention and control groups among prefrail and advanced-frailty participants. The numbers show that eight prefrail participants had to receive the intervention to prevent one of them becoming a faller (number needed to treat [NNT] = 7.9 [95% CI: 3.2 to 14.4]). Respectively, three advanced-frailty participants had to receive the intervention to prevent one of them becoming a faller (NNT = 2.6 [95% CI: 1.8 to 5.8]). The numbers of fallers per person-years are also shown in Table 11. Among prefrail participants the intervention group had 0.51 [95% CI: 0.35 to 0.72] fallers per person-years and the control group had 0.62 [95% CI: 0.39 to 0.93] fallers per person-years (IRR=0.83 [95% CI: 0.48 to 1.42]). Among advanced-frailty participants the intervention group had 0.50 [95% CI: 0.33 to 0.73] fallers per person-years and the control

group had 1.09 [95% CI: 0.69 to 1.63] fallers per person-years (IRR=0.46 [95% CI: 0.26 to 0.80]).

Table 11. Numbers of fallers in respect of years of exposure shown separately in intervention and control groups among prefrail and advanced-frailty participants.

	Intervention N=129	**Control N=65**
Number of participants		
Prefrail	73	38
Advanced frailty	56	27
Total years of exposure		
Prefrail	64.8	35.8
Advanced frailty	52.2	21.2
Fallers, n (%)		
Prefrail	33 (45.2)	22 (57.9)
Advanced frailty	26 (46.4)	23 (85.2)
Number of fallers per person years (95% CI)		
Prefrail	0.51 (0.35 to 0.72)	0.62 (0.39 to 0.93)
Advanced frailty	0.50 (0.33 to 0.73)	1.09 (0.69 to 1.63)

5.5 FALLS AMONG PATIENTS WITH DEMENTIA (STUDIES III AND IV)

Of the 194 participants in the study, 103 did not fall during the 12 months of follow-up, 34 fell once, and 57 fell two or more times (Figure 12). The persons having experienced a fall or falls in the preceding year of the study fell more than those not having a fall history in the preceding year.

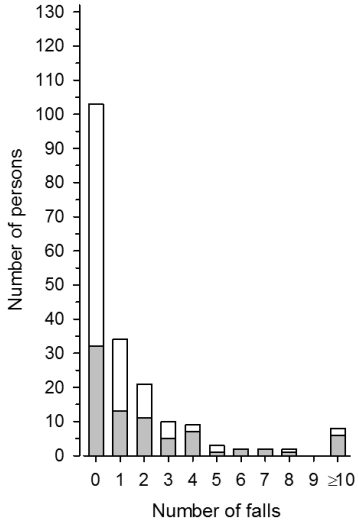

Figure 12. Number of participants according to the number of falls during the 12 months of follow-up. White parts of the columns reflect the persons with no falls in the year preceding the follow-up period; gray parts reflect the persons with a fall history in the preceding year.

The total number of falls was 355, of which half happened in the afternoon and the rest happened equally during evenings, nights and mornings. Stumbling (n=61), dizziness (n=37), and weakness of legs (n=18) were the most common reasons for a fall as reported by spouses of participants. However, the spouses could not state the cause for falling in most cases (Figure 13).

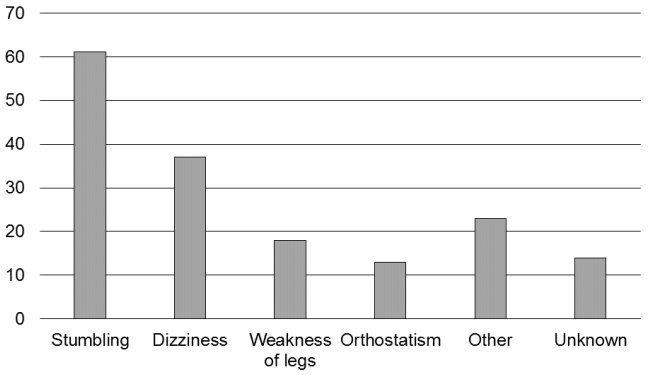

Figure 13. Numbers of cases and reasons for falling.

There were 123 injuries, 50 emergency department visits, and 13 fractures as consequences of the falls (Figure 14).

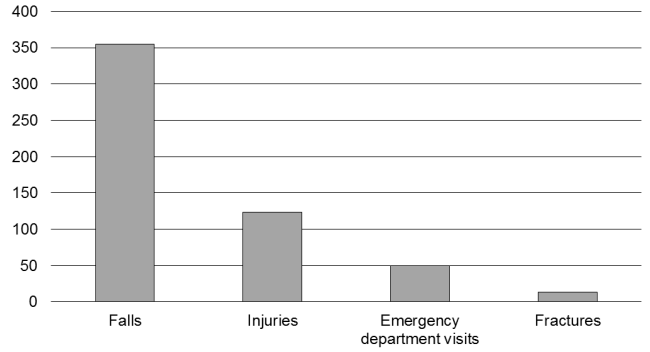

Figure 14. Numbers of falls, injuries, visits to emergency departments and fractures.

Protective and risk factors of falls

A prior fall (or falls) during the year preceding the study was a great risk factor of falls (IRR 2.71 [95% CI: 2.13 to 3.44]). In respect of MMSE, those participants scoring around 10 points had the greatest risk of falls (Figure 15).

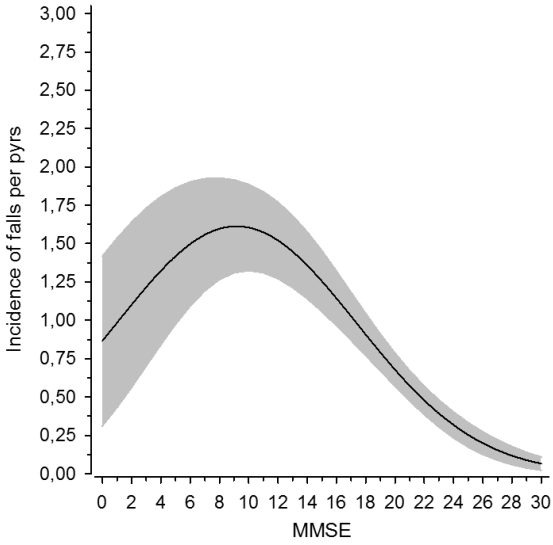

Figure 15. Incidence of falls per person-years (pyrs) according to the Mini-Mental State Examination (MMSE) score (Folstein et al. 1975).

An increasing number of regular drugs was associated with a greater incidence of falls (Figure 16).

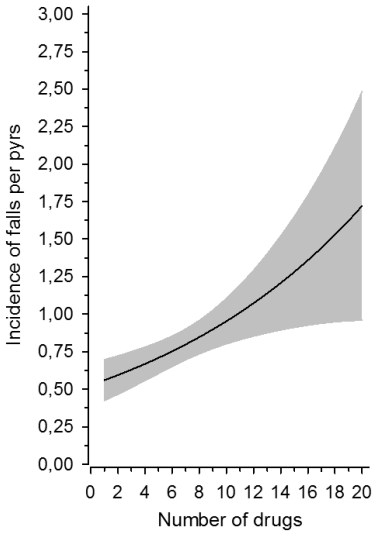

Figure 16. Incidence of falls per person-years (pyrs) according to the number of regularly used drugs.

The associations between physical features and the IRRs of falls (per 1-SD; adjusted for age, sex, and intervention) are presented in Figure 17. Better

scores for all the measured physical features had a protective association as regards falls. Higher FIM motor scores (IRR 0.49, 95% CI 0.45 to 0.54), SPPB scores (IRR 0.62, 95% CI 0.56 to 0.69), higher points in the SPPB balance test (IRR 0.79, 95% CI 0.70 to 0.88), faster walking speed (IRR 0.54, 95% CI 0.48 to 0.60), better scores in the Timed Up and Go test (IRR 0.46, 95% CI 0.3 to 0.54), and higher MNA scores (IRR 0.68, 95% CI 0.63 to 0.75) at baseline were all associated with a lower number of falls.

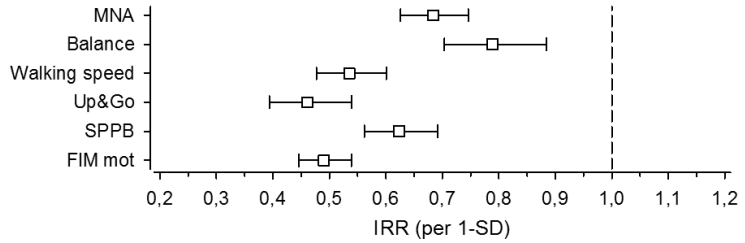

Figure 17. Associations between physical features and incidence rate ratios (IRRs) of falls (per 1-SD; adjusted for age, sex, and intervention). Balance=Balance test in SPPB; FIM=Functional Independence Measure (Pollak et al. 1996); MNA=Mini-Nutritional Assessment (Guigoz et al. 2002); SD=standard deviation; SPPB=Short Physical Performance Battery (Guralnik et al. 1994); Up&Go=Timed Up & Go test measuring chair mobility and walking (Podsiadlo & Richardson 1991); Walking speed=walking speed test in SPPB.

Figure 18 presents the relationship between diseases and the IRRs of falls (adjusted for age, sex, and intervention). Of the diseases, COPD (IRR 2.18, 95% CI 1.33 to 3.56), osteoarthritis (IRR 1.86, 95% CI 1.31 to 2.63), and diabetes mellitus (IRR 1.59, 95% CI 1.23 to 2.06) increased the IRR, whereas cancer (IRR 0.56, 95% CI 0.40 to 0.80) and hypertension (IRR 0.67, 95% CI 0.53 to 0.85) seemed to have a protective association with falls.

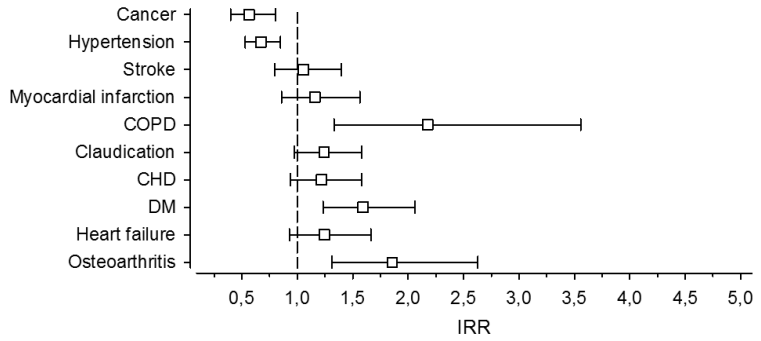

Figure 18. The association between diseases and the incidence rate ratios (IRRs) of falls (adjusted for age, sex, and intervention). CHD=coronary heart disease; COPD=chronic obstructive pulmonary disease; DM=diabetes mellitus

Figure 19 presents the relationship between drugs and the IRRs of falls (adjusted for age, sex, and intervention). Opioids (IRR 4.27, 95% CI 2.92 to 6.24), psychotropics (IRR 1.69, 95% CI 1.34 to 2.12), and DAPs (IRR 1.51, 95% CI 1.19 to 1.92) increased the IRR, whereas antihypertensive medication (IRR 0.68, 95% CI 0.54 to 0.85) had a protective association with falls.

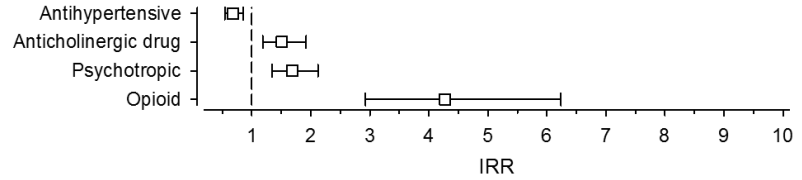

Figure 19. The effects of drugs on the incidence rate ratios (IRRs) of falls (adjusted for age, sex, and intervention).

Exercise modifies the risk of falls associated with fall-related drugs

The association between drugs and falls was compared in the intervention and control participants. Figure 20 presents the IRRs of falls during the 12 months of follow-up among participants with and without antihypertensives, psychotropics, DAPs, or polypharmacy, in intervention and control participants. (The IRRs and 95% CIs are crude figures.)

Among participants without antihypertensives, the control group had 0.9 falls per person-year (95% CI 0.6 to 1.2) and the intervention group had 1.2 falls per person-year (95% CI 1.0 to 1.4). Among participants with antihypertensives, the control group had 1.5 falls per person-year (95% CI 1.2 to 1.8) and the intervention group had 0.5 falls per person-year (95% CI 0.4 to 0.6) ($p=0.067$ for medication, $p<0.001$ for group, $p<0.001$ for interaction).

Among participants without psychotropics, the control group had 0.8 falls per person-year (95% CI 0.6 to 1.0) and the intervention group had 0.7 falls per person-year (95% CI 0.6 to 0.9). Among participants with psychotropics, the control group had 2.0 falls per person-year (95% CI 1.6 to 2.5) and the intervention group had 0.7 falls per person-year (95% CI 0.6 to 0.9) ($p=0.071$ for medication, $p<0.001$ for group, $p<0.001$ for interaction).

Among participants without DAPs, the control group had 1.2 falls per person-year (95% CI 1.0 to 1.4) and the intervention group had 0.6 falls per person-year (95% CI 0.5 to 0.7). Among participants with DAPs, the control group had 1.5 falls per person-year (95% CI 1.0 to 2.1) and the intervention group had 1.1 falls per person-year (95% CI 0.8 to 1.3) ($p=0.014$ for medication, $p<0.001$ for group, $p=0.97$ for interaction).

Among participants without polypharmacy, the control group had 1.0 falls per person-year (95% CI 0.8 to 1.3) and the intervention group had 0.6 falls per person-year (95% CI 0.5 to 0.8). Among participants with polypharmacy, (≥9 regular drugs) the control group had 1.9 falls per person-year (95% CI 1.4

to 2.4) and the intervention group had 1.0 falls per person-year (95% CI 0.8 to 1.3) (p=0.23 for medication, p<0.001 for group, p=0.17 for interaction).

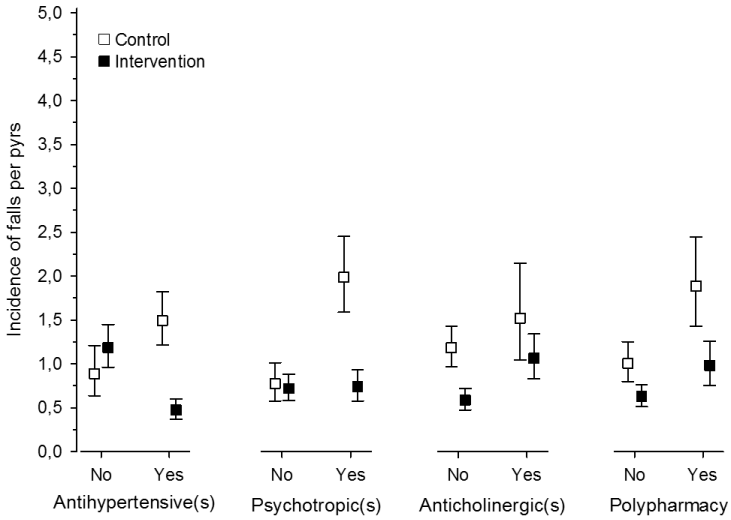

Figure 20. The incidence rate ratios of falls during the 12 months of follow-up per person-years (pyrs) among participants with and without antihypertensives, psychotropics, drugs with anticholinergic properties, or polypharmacy, in intervention and control participants.

6 DISCUSSION

6.1 MAIN FINDINGS

Both the HBS and the modified WHI-OS (physical frailty) measures identified 7.3% of the men as frail, whereas the FI identified significantly more men as frail (17.9%). The men identified as frail by various measures overlapped only moderately. All three frailty measures predicted more fallers, poorer HRQoL, and greater mortality among the frail men than among those who were prefrail or robust. The HBS and WHI-OS measures predicted a higher mortality rate in the frail group than did the FI measure. The findings suggest that various frailty measures can be used to identify people at risk, and they may be based on a simple questionnaire. All of them can be used to predict major outcomes such as mortality, HRQoL, and falls.

The results of the FINALEX study suggest that long-term and intensive exercise intervention may significantly slow down the decline of physical functioning in persons with AD, independently of the stage of frailty. The number of falls was also significantly reduced among both advanced frailty and prefrail participants in the intervention groups compared with their respective control groups.

Half of the falls in the FINALEX study occurred in the afternoon and the most commonly stated reasons for falls were stumbling, dizziness, and weakness of the legs. Among persons with AD, good nutritional status and physical functioning showed a protective association against falls. Regular use of DAPs, psychotropics, and opioids, and a higher total number of drugs used were associated with a greater number of falls. Certain diseases (osteoarthritis, diabetes, and COPD) were also associated with a greater number of falls. Unexpectedly, both hypertension and use of antihypertensive medication were associated with a lower number of falls. Participants with an MMSE score of around ten points were more prone to fall than those with lower or higher MMSE scores. The risk of falls among persons with AD using psychotropic medication or antihypertensive medication was significantly favorably modified by exercise intervention. However, exercise intervention did not modify the risk of falls among those using DAPs, or polypharmacy.

6.2 PROGNOSIS OF FRAILTY

In Study I, the baseline characteristics of the Helsinki Businessmen Study showed that the frail men, according to the HBS measure (Sirola et al. 2011), the modified WHI-OS measure (Woods et al. 2005), and the FI measure (Mitnitski et al. 2001) had several comorbidities. However, the frail participants according to the HBS and modified WHI-OS measures showed lower exercise levels, more weight loss, and lower BMI compared with frail individuals according to the FI measure. These baseline characteristics of participants according to both modified Fried criteria (HBS and modified WHI-OS) and the FI measure present similar features of frailty to those described previously, as the frail participants were older, had lower BMI, had more comorbidities according to the Charlson comorbidity index (Charlson et al. 1987), had more severe memory disturbances, and had more musculoskeletal diseases than prefrail and not frail participants (Fried et al. 2001, Rockwood et al. 2004, Woods et al. 2005). This suggests that these questionnaire-based frailty measures can be used to identify frail persons.

The prevalence of frailty in Study I was higher when investigated with the FI than with the two phenotypic measures. Both phenotype-based measures (HBS and modified WHI-OS) revealed a frailty prevalence of 7%, which is consistent with the results of earlier studies involving Fried criteria (Collard et al. 2012). There were only small differences between HBS and modified WHI-OS measures. However, only 70.7% of the men identified as frail by HBS and modified WHI-OS measures overlapped. The finding suggests that defining frailty is very challenging and it is highly important to cautiously choose the appropriate measure to assess frailty. The prevalence of frailty was 18% according to the FI, being similar to the result in a previous study involving the same measure (Rockwood et al. 2004). In line with the results of an earlier study (Collard et al. 2012), the FI yielded a greater prevalence of frailty than the physical frailty measures. In a systematic review the prevalence of frailty varied from 4.0% to 59.1% among home-dwelling persons, according to various frailty definitions (Collard et al. 2012). Studies involving physical frailty definitions such as the Fried criteria (Fried et al. 2001) and its modifications (Collard et al. 2012) yielded the lowest prevalence values. Two recent studies on various frailty measures revealed that phenotype-based measures identified fewer participants as frail than the FI measure (Malmstrom et al. 2014, Widagdo et al. 2015), as in Study I. The prevalence rate yielded by the FI with only 20 items in Study I is similar to those in studies involving FIs with 39 (Widagdo et al. 2015) or 25 (Malmstrom et al. 2014) items. This similarity in frailty prevalence values between these studies suggests that the FI can also contain only 20 items.

The two phenotype-based frailty measures and the FI measure compared in Study I predicted more fallers, poorer HRQoL, and greater mortality among frail men than among prefrail and not frail men. Previous studies have yielded similar findings, as found separately with the Fried criteria (Fried et al. 2001,

Ensrud et al. 2007, Widagdo et al. 2015, Kojima et al. 2016b), with the WHI-OS measure (Woods et al. 2005), with the HBS measure (Sirola et al. 2011), and with the FI measure (Mitnitski et al. 2001, Rockwood & Mitnitski 2007, Fang et al. 2012, Hubbard et al. 2014, Widagdo et al. 2015). The prognostic significance of the three frailty measures did not differ from each other as regards falls and HRQoL, but the mortality rate was lower in the frail group according to the FI measure compared with the frail groups according to the HBS and modified WHI-OS measures. There were no differences in weight change among the different frailty stages according to any of the compared frailty measures. Weight change is associated with frailty (Fried et al. 2001), but to my knowledge only one study (Sirola et al. 2011) has been carried out to investigate whether or not frailty predicts weight change, and there were no significant associations.

These findings justify all these definitions of frailty. Various measures approach the concept of frailty from different perspectives but still predict important outcomes. This study does not indicate a preference towards any of these frailty measures over the others. All of them offer prognostic validity albeit they identify different persons as frail. Any of them can be applied depending on the intended use. The FI might be used when needing a sensitive measure, whereas phenotype-based measures could be better options when screening for persons in need of exercise intervention.

6.3 FRAILTY IN MODIFYING THE EFFECTS OF EXERCISE IN DEMENTIA

Among participants in the FINALEX study frailty status was consistently and logically associated with gender, physical functioning, and stage of dementia. The baseline characteristics of the persons in our advanced frailty and prefrail groups were comparable to those in previous studies (Gillette-Guyonnet et al. 2000, Fried et al. 2001, Robertson et al. 2013). There were fewer females in the prefrail groups and the participants used less medication than those in the advanced frailty groups. Also, in line with the findings in previous studies (Robertson et al. 2013) the results of the FINALEX study suggested that frailty becomes more prevalent when dementia advances. Malnutrition is common among frail persons (Cadore et al. 2013b)), and in this study the proportions of well-nourished participants were lower in the advanced frailty groups than in the prefrail groups.

It has been suggested that exercise benefits frail persons by improving physical functioning (Chin A Paw et al. 2008, Theou et al. 2011, Chou et al. 2012), which is in line with the finding in Study II. Other researchers have suggested that exercise intervention could benefit prefrail persons more than frail persons (Faber et al. 2006). In contrast to this finding, exercise intervention seemed to benefit the AFI group even earlier than the PRI group in respect of FIM score changes. The baseline FIM scores showed that the PRI

group had better physical function than the AFI group at the beginning of the study. Thus, for the AFI group there was a greater potential to enhance physical function. However, in line with findings in this study, a *post-hoc* analysis of the LIFE-P study suggested that exercise intervention benefited frail persons more than non-frail persons (Cesari et al. 2015). In the present study, the number of falls was significantly lower in the PRI and AFI groups than in the PRC and AFC groups. Previous studies have shown similar results in reducing the number of falls via exercise intervention (Cadore et al. 2013b). Such benefits in both intervention groups probably resulted from diverse, frequent, and long-term exercise intervention including balance training, which has also showed the most benefit in previous studies (Theou et al. 2011).

6.4 FALLS AMONG PARTICIPANTS WITH DEMENTIA

In Study III all the FINALEX participants were classified into groups of none, one, and two or more falls. Participants in the group of two or more falls were older, their systolic blood pressure was lower, vision problems were more common, and they had more severe dementia according to CDR than those with no falls or only one. Also, their mobility limitations according to SPPB rating, and physical functioning according to FIM were worse than among groups of no falls or only one. Earlier studies in which non-fallers and fallers have been compared have revealed similar characteristics (Horikawa et al. 2005, Salva et al. 2012, Meuleners et al. 2016).

Consistent with previous research findings (Allan et al. 2009, Salva et al. 2012, Meuleners et al. 2016) a fall history was a risk factor of falls. An MMSE score in the range of 22–30 was a risk factor of falls in older persons with subtle cognitive impairment in a previous study (Gleason et al. 2009). However, the present study also involved persons with very low MMSE scores and the results suggest that persons scoring around ten points in MMSE are the most prone to falls. There were fewer falls among persons with extremely low MMSE scores, probably because they walk less.

The findings in this study indicate that better physical functioning, and lower mobility limitations are protective factors against falls, which is in line with the results of previous studies (AGS 2001, Allan et al. 2009, Salva et al. 2012). A higher MNA score was a protective factor in this study, and previously the MNA score has been found to be significantly lower among fallers than non-fallers (Salva et al. 2012).

Osteoarthritis, COPD, and diabetes mellitus (DM) were risk factors of falls in this study. Arthritis has been found to be a risk factor of falls among older people (AGS 2001). A systematic review and meta-analysis showed diabetes to be a fall risk factor (Yang et al. 2016), which is in accordance with the finding in this study among people with AD. COPD was found to be a fall risk factor in a study among older women (Lawlor et al. 2003). The present findings indicate that these diseases may also be risk factors of falls among people with AD.

Psychotropics and polypharmacy have shown strong risk associations with falls among older people (AGS 2011). Accordingly, in the present study the risk of falls increased when the number of drugs used increased. In line with the results of other studies among persons with dementia (Horikawa et al. 2005, Kudo et al. 2009), psychotropics increased the risk of falls in this study. An important finding in this study was the fact that the use of opioids appeared to be a major risk factor of falls. A previous systematic review included one study (Kelly et al. 2003) in which opioids were associated with falls and one study (Ensrud et al. 2002) without this association (Hartikainen et al. 2007). Another study revealed no significance difference between users and non-users of opioids among community-dwelling older men (Krebs et al. 2016). One study on the association between opioids and falls among persons with AD showed an increased risk of falls in crude numbers, but the risk did not persist after adjustment for occupational social class (Tolppanen et al. 2016).

In this study both hypertension and antihypertensive medication had a protective association as regards falls, which is in contrast to earlier research data (Hartikainen et al. 2007, Gangavati et al. 2011). Symptomatic orthostatic hypotension has been reported to be a risk factor of falls (Allan et al. 2009). Those persons with active diagnosis of hypertension, and antihypertensive medication, may be robust persons having higher blood pressure, whereas those persons with lower blood pressure may be persons with more severe dementia having a "terminal decline" in their blood pressure (Benetos et al. 2016). The fact that persons with two or more falls had lower blood pressure than persons with fewer falls supports this hypothesis. However, even frail patients have been suggested to benefit from antihypertensive drugs in a recent study among older hypertensive persons (Williamson et al. 2016). Their prognosis was improved by targeting systolic blood pressure to <120 mmHg without increasing falls (Williamson et al. 2016). However, their orthostatic hypotension was regularly monitored over the trial and their antihypertensives were accordingly modified (Supiano & Williamson 2017).

Concerning interventions in reducing falls, a meta-analysis revealed multifactorial and exercise interventions to be most effective (Chang et al. 2004). Reducing psychoactive medication and reducing the number of drugs can also be used as interventions among community-dwelling older people, as previously stated (AGS 2011). However, there is a scarcity of studies concerning forms of intervention to reduce falls among people with dementia. The results of recent meta-analyses have suggested that exercise may prevent falls among people with known dementia and cognitive impairment (Burton et al. 2015, Chan et al. 2015). In Study IV possible interactions between exercise intervention and FRDs were explored. Adding to the literature, exercise intervention was found to interact with psychotropic and antihypertensive drugs. Better circulation could be the mechanism in respect of antihypertensives, as exercise induces the calf muscles to work more effectively, which enhances blood flow to the heart and brain. Thus, the risk of orthostatic hypotension may be reduced. Better mobility and balance as a

result of exercise training serves as one explanation as regards both types of medication. There was no interaction effect between exercise and DAPs, although exercise intervention was associated with a decreased risk of falls among both DAP users and nonusers. A similar pattern was found among those with and without polypharmacy.

The findings in this study indicate that among persons with dementia certain types of medication may increase the risk of falls. However, it is possible to completely compensate for this by means of exercise among users of psychotropic and antihypertensive drugs. Thus, exercise should be encouraged especially among dementia patients with hypertension. Those with dementia using psychotropic drugs should also be encouraged to exercise, although eliminating or reducing psychotropic drug use may be the primary aim in decreasing the risk of falls. Dementia patients with polypharmacy and those using DAPs should also be encouraged to exercise, although their risk of falls is not completely compensated by exercise. Thus, reducing polypharmacy and eliminating the use of DAPs should be the primary aim in these cases.

6.5 STRENGTHS AND LIMITATIONS

Helsinki Businessmen Study

The Helsinki Businessmen Study has several strengths. It is one of the longest cohort studies. Characterization of the participants is thorough, and the response rates have been high. When investigating mechanisms regarding gender, race, and socioeconomic status, confounding is reduced because of the homogeneity of the participants. There are also some limitations in the Helsinki Businessmen Study. Generalization to other populations is limited because of the homogeneity and characteristics of the participants. The analyses are based solely on responses to postal questionnaires, with their inherent limitations. However, the educational status of the men was high, and thus the answers they gave may be more reliable than those provided by the general population (Schlademann et al. 2008). The number of falls was asked about and the participants responded solely on the basis of their memories of the previous year. On the other hand, fallers were defined as those having had at least one fall in the previous year. Thus, the outcome measure in Study I did not change according to the actual number of falls remembered within the previous year. The FI score was determined using 20 items, which is fewer than in several previous studies (Rockwood & Mitnitski 2007). However, no absolute threshold of items has been set and this study provides information on how low the number of items can be. The FI is a continuous score (Mitnitski et al. 2001), but in Study I it was defined in groups of not frail, prefrail and frail, with cut-off points of 0.08 for prefrail and 0.25 for frail, which have been used previously (Song et al. 2010). This categorization to not frail, prefrail and frail enabled comparison of FI and phenotype measures. Some of the groups

are relatively small because of the small sample size. Small groups of participants are particularly evident in the Venn diagram presenting overlapping of the frail groups according to the three frailty measures. On the other hand, it is possible to observe differences in the frailty measures even with small numbers of participants.

FINALEX

The FINALEX study (a randomized controlled trial [RCT]) has several strengths. All participants had a diagnosis of AD based on the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association's (NINCDS-ADRDA) criteria for diagnosis of probable AD (McKhann et al. 1984) and they were confirmed by a geriatrician. Intervention was highly coordinated and each training session was supervised by a physiotherapist. The intervention was also frequent (twice a week) and long-term (12 months). It was implemented by physiotherapists in primary care and did not increase the total costs of health and social services (Pitkala et al. 2013). The spouses kept fall diaries, which served to assess the falls. The fall diaries were continuously filled in by the spousal caregivers. A diary is a highly sensitive method in recording falls accurately (Hannan et al. 2010), giving reliability to the findings. The types of medication used and comorbidities were confirmed both from spousal caregivers and medical records. The baseline characteristics of the intervention and control groups were comparable and they presented similar features as seen in previous studies among persons with dementia (Allan et al. 2009), giving reliability to the findings in this patient group. In Study II, definition of the stage of frailty was based on Fried criteria, which predict major endpoints such as disabilities and death (Fried et al. 2001). In Studies III and IV, the features behind falls were investigated in a prospective manner.

The FINALEX study also has several limitations. All the participants were community-dwelling voluntary Caucasians living with their spousal caregivers in their homes. Generalization of the results to other populations should be approached with appropriate caution. The power of the study was decreased because of the small sample size. The study was not blinded. However, the study nurses collecting the data were not informed about the exact intervention and primary outcome measures and they were not researchers in the study. Moreover, the spousal caregivers were also not aware of the study hypothesis, and their evaluations were used to assess the FIM scores (Pollak et al. 1996) and falls of the participants. The control group received high-quality community care, which probably decreased differences between the original intervention and control groups in Studies II and IV. Although the types of medication used at the end of the 12-month intervention period were not confirmed, the study intervention was not intended to change them. Studies II and IV involved subgroup analyses of the original RCT, and therefore the groups compared were not original randomized groups. In

addition, the intervention groups in these analyses contained both home-based and group-based participants. However, the individual training time for both home-trainers and group-trainers was approximately one hour twice a week. In Study II, the participants could not be divided into the traditional three frailty-stage groups of robust, prefrail, and frail (Fried et al. 2001) because of the small number of participants. However, the inclusion criteria stated that all participants had to have at least one sign of frailty. Thus, it can be argued that all participants were either prefrail or frail persons. The intervention decreased the number of falls among intervention participants. Thus, in Study III, the total number of falls was lower than expected among persons with AD, and this may also have modified the features of the falls. However, the findings in Study III were adjusted for age, sex, and intervention as regards the risk factors of falls. The number of falls among the controls (Pitkala et al. 2013) was comparable to those in previous studies among persons with AD (Allan et al. 2009). The SPPB test was modified from the original test to give time and to better suit participants with dementia. It gave respective scores as in the original test and showed logically that performance in the SPPB test was lower among fallers than non-fallers. Thus, it can be argued that this modified test probably reflects well the points that each participant could have scored in the original SPPB.

7 CONCLUSIONS

Both phenotype frailty measures and the FI can be used to identify frail people. Simple and easy-to-use frailty phenotype measures (e.g. Fried criteria) can be used to screen for those in need of exercise intervention, whereas the more laborious FI method could be used when assessing patients in detail in cases where more comprehensive geriatric intervention may be necessary.

Intensive and long-term exercise intervention may benefit persons with AD, independently of their frailty stage, in respect of physical functioning and falls. In addition to previously known risk factors of falls among people with AD (a history of falls, older age, female gender, disability, use of psychotropic drugs, and decreased physical activity), this study revealed that use of anticholinergic drugs and opioids, and polypharmacy, lower systolic blood pressure, COPD, DM, and osteoarthritis are also risk factors of falls. In contrast to prior studies, the results of this study also suggested that hypertension and antihypertensive medication may be associated with a reduced risk of falls.

When exploring the features of falls in detail among people with AD this study found that most falls occurred in the afternoon, and stumbling, dizziness, and weakness of the legs were the most common reasons for a fall. Those persons with an MMSE score around ten points fell most, every third fall led to injury, every seventh fall led to an emergency department visit, and 4% of falls led to fracture. Exercise intervention has the potential to modify favorably the risk of falls among people with AD using antihypertensives, psychotropics and DAPs, and those with polypharmacy. Among those AD cases using antihypertensive or psychotropic drugs, exercise totally compensates for their risk of falls.

8 IMPLICATIONS FOR CLINICAL PRACTICE AND FUTURE RESEARCH

Experts have not reached a consensus of opinion on the definition of frailty. However, it can be argued that different frailty measures could be used for different purposes. Simple physical frailty measures may provide a better tool to screen for those who could benefit from exercise intervention, whereas the FI can provide more detail but is a more laborious measure. Questionnaires may be used for screening by means of both phenotype measures and the FI. Frailty is one of the major health problems and needs to be carefully defined. Thus, more studies are needed to compare various frailty measures on the basis of both Fried criteria and the FI. In addition, questionnaire-based measures could be compared with clinically assessed measures in the same study population in respect of identifying prefrail and frail persons as well as predicting outcomes such as falls and mortality.

Persons with AD should be encouraged to undertake exercise training regardless of their stage of frailty. More RCTs are needed in these patient groups to confirm the present findings.

Poor physical functioning, certain diseases such as COPD and DM, and polypharmacy as well as certain types of drugs such as DAPs and psychotropics increase the risk of falls. Exercise should be encouraged in all cases to enhance physical functioning. Long-term use of DAPs and psychotropics, as well as polypharmacy, should be avoided. Excessive drug use should be reduced if possible. Further studies with more participants are needed to establish the associations between various drugs, diseases and physical conditions, and falls among people with dementia.

Those persons in particular who need long-term use of DAPs or psychotropic drugs should be encouraged to undertake exercise training to reduce the risk of falls. Further studies including more participants are needed to confirm these findings. In addition, randomized controlled trials could also serve to investigate possible interactions between exercise and other drugs, as well as various diseases, on the risk of falls.

Exercise intervention studies should be repeated in different settings and among persons of different cultures and origins to determine whether the results are generalizable.

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APPENDICES

Appendix I. Helsinki Businessmen Study questionnaire in 2000 (in Finnish).

JOHTAJATARKASTUKSISSA KÄYNEIDEN SEURANTATUTKIMUS VUONNA 2000

Aluksi muutama kysymys nykyisistä elinoloistanne ja –tavoistanne:
(ympyröikää vastauksenne kirjain tai kirjoittakaa vastaus viivalle)

1. Oletteko vielä työelämässä
   a) kyllä b) en. Olen eläkkeellä vuodesta _____
2. Jos olette eläkkeellä, jäittekö **alunperin**
   a) vanhuuseläkkeelle
   b) varhennetulle vanhuseläkkeelle
   c) osa-aikaeläkkeelle
   d) työkyvyttömyyseläkkeelle
   e) työttömyyseläkkeelle
   f) minulla oli henkilökohtainen eläkesopimus
3. Asutteko nykyisin
   a) kotona
   b) pysyvästi palvelutalossa
   c) pysyvästi vanhainkodissa
   d) pysyvästi hoivakodissa
   e) pysyvästi sairaalassa
4. Mikä on nykyinen siviilisäätynne
   a) avioliitossa tai avoliitossa
   b) leski, _____ vuotta
   c) eronnut, _____ vuotta
   d) naimaton
5. Tupakoitteko nykyisin?
   a) en ole koskaan tupakoinut
   b) lopetin vuonna _____
   c) kyllä tupakoin
6. Montako vuotta olette elämänne aikana tupakoinut?
   _____ vuotta
7. Vain **nykyisin** tupakoiville: miten paljon poltatte keskimäärin päivässä?
   a) savukkeita _____ kpl/pv
   b) piippua _____ piipullista/pv
   c) sikareja _____ kpl/pv
   d) pikkusikareja _____ kpl/pv
8. Mikä on ollut keskimäärin alkoholin **viikkokäyttönne** viimeksi kuluneen vuoden aikana?
   a) oluttu _____ pullollista/viikko
   b) viiniä _____ lasillista/viikko
   c) väkeviä juomia _____ grogia (ravintola-annosta vastaava määrä/viikko)
9. Harrastatteko liikuntaa säännöllisesti viikottain?
   a) en
   b) kyllä _____ tuntia/viikko

10. Kuinka monta kertaa viikossa harrastatte hengästymistä ja hikoilua aiheuttavaa liikuntaa _____ kertaa viikossa
11. Mikä on

- nykyinen painonne _____ kg?
- viimeisin verenpainelukemanne _____/_____
- viimeisin kolesterolilukemanne (S-kol) _____ mmol/l
- viimeisin verensokerilukemanne (B-gluk) _____ mmol/l

Seuraavaksi muutama kysymys mahdollisista sairauksista ja lääkkeistä:

12. Onko Teillä jokin pitkäaikainen (krooninen) sairaus, vika tai vamma?
    a) ei
    b) kyllä, mikä tai mitkä
    _____
    _____
    _____
13. Jos Teillä on krooninen sairaus, vika tai vamma, heikentääkö se toimintakykyänne?
    a) ei b) kyllä
14. Kuinka monta viikkoa yhteensä olette viimeisen **5 vuoden aikana** ollut sairaalahoidossa
    a) en yhtäkään
    b) _____ viikkoa

Onko Teillä ollut tai on jotain seuraavista (ympyröikää vastauksenne)

15. muistihäiriöitä ei kyllä, vuonna _____
16. aivohalvaus tai aivoverenkiertohäiriö ei kyllä, vuonna _____
17. kohonnut verenpaine ei kyllä, vuonna _____
18. sepelvaltimotauti ei kyllä, vuonna _____
19. sydämen vajaatoiminta ei kyllä, vuonna _____
20. krooninen keuhkosairaus ei kyllä, vuonna _____
21. alaraajojen verenkiertohäiriö ei kyllä, vuonna _____
22. diabetes (sokeritauti) ei kyllä, vuonna _____
23. syöpä ei kyllä, vuonna _____
24. tuki- ja liikuntaelinten sairaus ei kyllä, vuonna _____
25. mielenterveyden häiriö ei kyllä, vuonna _____
26. muu pitkäaikainen sairaus tai vamma, mikä ei kyllä, vuonna _____
    _____
27. Käytättekö säännöllisesti jotain lääkettä (**myös käsikauppalääkkeet**, esim. aspiriini)
    a) ei
    b) kyllä _____
28. Kirjoittakaa tähän säännöllinen lääkityksenne (viimeisen 6 kuukauden aikana käytetty): sekä resepti- että käsikauppalääkkeet, **NIMI JA ANNOS**
    _____
    _____
    _____
    _____

Seuraavat kysmykset pyrkivät mittaamaan toimintakykyänne:

29. Onko terveytenne yleisesti ottaen (ympyröikää yksi numero)
    1 erinomainen
    2 varsin hyvä
    3 hyvä
    4 tyydyttävä
    5 huono
30. Jos vertaatte nykyistä terveydentilaanne vuoden takaiseen, onko terveytenne yleisesti ottaen (ympyröikää yksi numero)
    1 tällä hetkellä paljon parempi kuin vuosi sitten
    2 tällä hetkellä jonkin verran parempi kuin vuosi sitten
    3 suunnilleen samanlainen
    4 tällä hetkellä jonkin verran huonompi kuin vuosi sitten
    5 tällä hetkellä paljon huonompi kuin vuosi sitten

Seuraavassa luetellaan erilaisia päivittäisiä toimintoja. Rajoittaako terveydentilanne nykyisiin suoriutumistanne seuraavista päivittäisistä toiminnoista? Jos rajoittaa, kuinka paljon? (ympyröikää yksi numero joka riviltä)

	kyllä, rajoittaa paljon	kyllä, rajoittaa hiukan	ei rajoita lainkaan
31. Huomattavia ponnistuksia vaativat toiminnat (esimerkiksi juokseminen, raskaiden tavaroiden nostelu, rasittava urheilu)	1	2	3
32. Kohtuullisia ponnistuksia vaativat toiminnat, kuten pöydän siirtäminen, imurointi, keilailu	1	2	3
33. Ruokakassien nostaminen tai kantaminen	1	2	3
34. Nouseminen portaita useita kerroksia	1	2	3
35. Nouseminen portaita yhden kerroksen	1	2	3
36. Vartalon taivuttaminen, polvistuminen, kumartuminen	1	2	3
37. Noin kahden kilometrin matkan kävely	1	2	3
38. Noin puolen kilometrin matkan kävely	1	2	3
39. Noin 100 metrin matkan kävely	1	2	3
40. Kylpeminen tai pukeutuminen	1	2	3

Onko teillä viimeisen 4 viikon aikana ollut **ruumiillisen terveydentilanne takia** alla mainittuja ongelmia työssänne tai muissa tavanomaisissa päivittäisissä tehtävissänne? (ympyröikää yksi numero joka riviltä)

	Kyllä	ei
41. Vähensitte työhön tai muihin tehtäviin käyttämäänne aikaa	1	2
42. Saitte aikaiseksi vähemmän kuin halusitte	1	2
43. Terveydentilanne asetti teille rajoituksia joissakin työ- tai muissa tehtävissä	1	2
44. Töistänne tai tehtävistänne suoriutuminen tuotti vaikeuksia (olette joutunut esim. ponnistelmeaan tavallista enemmän)	1	2

Onko Teillä viimeisen 4 viikon aikana ollut **tunne-elämään liittyvien** vaikeuksien (esim. masentuneisuus tai ahdistuneisuus) takia alla mainittuja ongelmia työssänne tai muissa tavanomaisissa päivittäisissä tehtävissänne? (ympyröikää yksi numero joka riviltä)

	Kyllä	ei
45. Vähensitte työhön tai muihin tehtäviin käyttämäänne aikaa	1	2
46. Saitte aikaiseksi vähemmän kuin halusitte	1	2
47. Ette suorittanut töitänne tai muita tehtäviänne yhtä huolellisesti kuin tavallisesti	1	2

48. **Missä määrin** ruumiillinen terveydentilanne tai tunne-elämän vaikeudet ovat viimeisen 4 viikon aikana häirinneet tavanomaista (sosiaalista) toimintaanne perheen, ystävien, naapureiden tai muiden ihmisten parissa? (ympyröikää yksi numero)
    1 ei lainkaan
    2 hieman
    3 kohtalaisesti
    4 melko paljon
    5 erittäin paljon

49. Kuinka voimakkaita ruumiillisia kipuja Teillä on ollut viimeisen 4 viikon aikana? (ympyröikää yksi numero)
    1 ei lainkaan
    2 hyvin lieviä
    3 lieviä
    4 kohtalaisia
    5 voimakkaita
    6 erittäin voimakkaita

50. Kuinka paljon kipu on häirinnyt tavanomaista toimintaanne (kotona tai kodin ulkopuolella) viimeisen 4 viikon aikana? (ympyröikää yksi numero)
    1 ei lainkaan
    2 hieman
    3 kohtalaisesti
    4 melko paljon
    5 erittäin paljon

Seuraavat kysymykset koskevat sitä, miltä Teistä on tuntunut viimeisen 4 viikon aikaa. Merkitkää kunkin kysymyksen kohdalla se numero, joka parhaiten kuvaa tuntemuksianne.

Kuinka suuren osan ajasta olette viimeisen 4 viikon aikana… (ympyröikää yksi numero joka riviltä)

	koko ajan	suurimman osan aikaa	huomattavan osan aikaa	jonkin aikaa	vähän aikaa	en lainkaan
51. tuntenut olevanne täynnä elinvoimaa	1	2	3	4	5	6
52. ollut hyvin hermostunut	1	2	3	4	5	6
53. tuntenut mielialanne niin matalaksi, ettei mikään ole voinut teitä piristää	1	2	3	4	5	6
54. tuntenut itsenne tyyneksi ja rauhalliseksi	1	2	3	4	5	6
55. ollut täynnä tarmoa	1	2	3	4	5	6
56. tuntenut itsenne alakuloiseksi ja apeaksi	1	2	3	4	5	6
57. tuntenut itsenne ”loppuunkuluneeksi”	1	2	3	4	5	6
58. ollut onnellinen	1	2	3	4	5	6
59. tuntenut itsenne väsyneeksi	1	2	3	4	5	6

60. **Kuinka suuren osan ajasta** ruumiillinen terveydentilanne tai tunne-elämän vaikeudet ovat viimeisen 4 viikon aikana häirinneet tavanomaista sosiaalista toimintaanne (ystävien, sukulaisten, muiden ihmisten tapaaminen)? (ympyröikää yksi numero)
    1 koko ajan
    2 suurimman osan aikaa
    3 jonkin aikaa
    4 vähän aikaa
    5 ei lainkaan

Kuinka hyvin seuraavat väittämät pitävät paikkansa Teidän kohdallanne? (ympyröikää yksi numero joka riviltä)

	Pitää ehdotto-masti paikkansa	pitää enimmäk-seen paikkansa	en osaa sanoa	enimmäk-seen ei pidä paikkansa	ehdotto-masti ei pidä paikkansa
61. Minusta tuntuu, että sairastun jonkin verran helpommin kuin muut ihmiset	1	2	3	4	5
62. Olen vähintään yhtä terve kuin kaikki muutkin tuntemani ihmiset	1	2	3	4	5
63. Uskon, että terveyteni tulee heikkenemään	1	2	3	4	5
64. Terveyteni on erinomainen	1	2	3	4	5

65. Mikäli lähetämme Teille kutsun lisätutkimuksiin, oletteko mahdollisesti niihin halukas (verikokeet, pään magneettitutkimus) Meilahden sairaalassa. Tutkimukset ovat maksuttomia.
    a) kyllä b) en

Antamiani tietoja voidaan käyttää saatekirjeessä mainittuihin tutkimustarkoituksiin.

_____ _____

Paikka ja päivämäärä Allekirjoitus ja puhelinnumero

Tarkistattehan vielä, että olette vastannut kaikkiin kysymyksiin
PARHAAT KIITOKSET VASTAUKSISTANNE

Tarra **LUOTTAMUKSELLINEN**

Henkilötunnuksenne _____ - _____

Puhelinnumero, johon saamme ottaa tarvittaessa yhteyttä: _____

JOHTAJATARKASTUKSISSA KÄYNEIDEN SEURANTATUTKIMUS VUONNA 2005

Kiitämme halukkuudestanne osallistua tähän kirjekyselyyn.

HUOM: Erittäin tärkeä osa tätä kyselyä ovat muistiin ja aivoverenkiertohäiriöihin ja niiden taustatekijöihin liittyvät osat. Vaikkei näitä mielestänne olisi esiintynytkään, pyydämme Teitä kuitenkin käymään kysymykset läpi. Toivomme myös – jos kirjeen saaja ei itse pysty vastaamaan – että hänen läheisensä vastaisi ainakin näihin kysymyksiin.

Aluksi muutama kysymys asumiseenne, koulutukseen, muistiin ja mahdollisiin muistihäiriöihin liittyen:

(ympyröikää vastauksenne kirjain tai kirjoittakaa vastaus viivalle)

1. Asutteko nykyisin

a) kotona
b) pysyvästi palvelutalossa
c) pysyvästi vanhainkodissa
d) pysyvästi hoivakodissa
e) pysyvästi sairaalassa

2. Oletteko koskaan käyttänyt **säännöllisesti** seuraavia lääkkeitä? Jos kyllä, montako vuotta yhteensä

verenpainelääkkeet:	en	kyllä, _____ vuotta
kolesterolilääkkeet (esim. ns. statiinit)	en	kyllä, _____ vuotta
asetosalisyylihappo (aspiriini, disperin, primaspan jne.)	en	kyllä, _____ vuotta
tulehduskipulääkkeitä (esim. burana, ketorin, jne. HUOM: ei tarkoita panadol, para-tabs, paracetamol jne)	en	kyllä, _____ vuotta
sokeritauti (diabetes) lääkkeitä:	en	kyllä. _____ vuotta
vitamiini- tai hivenainevalmisteita	en	kyllä _____ vuotta
reumalääkkeitä	en	kyllä_____ vuotta

3. Onko Teillä oikeus seuraaviin erityiskorvattaviin lääkkeisiin (vaikka ette niitä tällä hetkellä käyttäisikään. **Numero näkyy KELA-kortissa**):

a) verenpainelääkkeet (numero 205)
b) sepelvaltimotaudin lääkkeet (numero 206)
c) sydämen vajaatoiminnan lääkkeet (numero 201)
d) astmalääkkeet (numero 203)
e) diabeteslääkkeet (numero 103)
f) kolesterolilääkkeet (numero 213)
g) Parkinsonin tauti (numero 110)
h) Kihti (numero 212)
i) Reuma (numero 202)

Jos kirjeensaajalla on diagnosoitu dementia, siirtykää kysymykseen 17

Appendix II. Helsinki Businessmen Study questionnaire in 2005 (in Finnish).

4. Millainen muistinne oli aikaisemmin(5-10 vuotta sitten) verrattuna ikätovereidenne muistiin omasta mielestänne

a) muistini oli selvästi parempi
b) muistini oli jonkin verran parempi
c) ei huomattavaa eroa
d) muistini oli jonkin verran huonompi
e) muistini oli selvästi huonompi

5. Oliko Teidän aikaisemmin vaikea muistaa tapahtumatietoja

a) aina tai lähes aina
b) usein
c) toisinaan
d) harvoin
e) ei koskaan

6. Onko muistinne nykyisin mielestänne keskimäärin huonompi kuin ikäisenne ystävänne tai asuinkumppaninne

a) ei, vaan muistini on selvästi parempi
b) ei, vaan muistini on jonkin verran parempi
c) en ole huomannut eroa
d) kyllä, muistini on jonkin verran huonompi
e) kyllä, muistini on selvästi huonompi

7. Onko Teidän mielestänne nykyisin vaikeampi painaa mieleen / oppia tuoreita tai uusia asioita

a) aina tai lähes aina
b) usein
c) toisinaan
d) harvoin
e) ei koskaan

8. Onko Teidän mielestänne nykyisin vaikeampi palauttaa mieleenne tuoreita / uusia asioita

a) aina tai lähes aina
b) usein
c) toisinaan
d) harvoin
e) ei koskaan

9. Onko Teidän mielestänne nykyisin vaikeampi palauttaa mieleen vanhoja asioita

a) aina tai lähes aina
b) usein
c) toisinaan
d) harvoin
e) ei koskaan

10. Onko Teidän nykyisin vaikea muistaa tapahtumatietoja

a) aina tai lähes aina
b) usein
c) toisinaan
d) harvoin
e) ei koskaan

11. Onko muistinne mielestänne heikentynyt

a) selvästi
b) jonkin verran
c) ei
d) en osaa sanoa

12. Osaatteko sanoa kokevatko läheisenne (puoliso / lapset) muistissanne tapahtuneen heikentymistä?

a) kyllä
b) jonkin verran
c) ei
d) en osaa sanoa

13. Mikäli vastasitte kysymykseen 12 myöntävästi eli koette muistinne heikentyneen, niin alkoivatko oireet

a) asteittain/ huomaamatta
b) suhteellisen nopeasti/ äkillisesti
c) en osaa sanoa

14. Kuinka pitkään olette kärsineet muistin heikkenemisestä

a) vähemmän kuin vuoden
b) yli vuoden
c) jo useiden vuosien ajan

15. Vaikuttaako muistihäiriö selviytymiseenne päivittäisistä toiminnoista

a) aina tai lähes aina
b) usein
c) toisinaan
d) harvoin
e) ei koskaan

16. Tarvitsetteko ulkopuolista apua muistihäiriön takia selviytyäksenne arkitoimista

a) aina tai lähes aina
b) usein
c) toisinaan
d) harvoin
e) en koskaan

Mistä selviytyäksenne? _____

17. Oletteko ollut lääkärin tutkimuksissa muistihäiriön takia

ei kyllä, vuonna_____, missä _____

18. Jos kyllä, onko lääkäri todennut Teillä

a) Alzheimerin taudin vuonna_____
b) verisuoniperäisen dementian vuonna_____
c) muun dementian vuonna_____

19. Onko Teille tehty pään tietokone- tai magneettikuvausta

ei kyllä, vuonna_____, syynä oli_____

20. Onko Teille tehty muistitestiä (MMSE)

ei kyllä, viimeksi pistemäärä oli ____/30 pistettä

21. Käytättekö tai oletteko käyttänyt jotain seuraavista lääkkeistä

a) Aricept, vuodesta _____
b) Exelon, vuodesta _____
c) Reminyl, vuodesta _____
d) Ebixa, vuodesta _____
e) jokin muu ns. Alzheimerlääke _____

Seuraavassa kysymyksiä mahdollisiin aivoverenkiertohäiriöihin liittyen:

22. Onko Teillä esiintynyt äkillinen puheen menetys tai häiriö kyllä ei

Jos kyllä, milloin ja missä hoidettiin _____

23. Onko Teillä esiintynyt äkillinen näön menetys kyllä ei

Jos kyllä, milloin ja missä hoidettiin _____

24. Onko Teillä esiintynyt äkillisiä kaksoiskuvia kyllä ei

Jos kyllä, milloin ja missä hoidettiin _____

25. Onko Teillä esiintynyt äkillistä toispuolista (käsi, jalka) pistelyä tai puutumista kyllä ei

Jos kyllä, milloin ja missä hoidettiin _____

26. Onko Teillä esiintynyt äkillistä **toispuolista** halvausoiretta tai heikkoutta kyllä ei

Jos kyllä, milloin ja missä hoidettiin _____

27. Onko Teillä esiintynyt äkillinen **ohimenevä** muistihäiriö. kyllä ei

Jos kyllä, milloin ja missä hoidettiin _____

28. Onko Teillä esiintynyt äkillistä huimausta tai äkillisiä tasapainohäiriöitä kyllä ei

Jos kyllä, milloin ja missä hoidettiin _____

29. **Pahin / vaikein** edellä kuvatun kaltainen kohtaus

a) minä vuonna _____
b) oireet: _____
c) milloin alkoi: päivällä / unessa / herätessä / ei tietoa

30. Onko lääkäri todennut Teillä aivoverenkiertohäiriön (aivohalvaus, aivoverisuonitukos, aivoverenvuoto, aivoinfarkti, TIA-kohtaus)? kyllä ei

Jos kyllä, minä vuonna:_____
Oireet:_____

31. Jäikö pysyviä oireita

a) ei
b) kyllä, mitä
_____

32. Oletteko kaatunut viimeksi kuluneen vuoden aikana

a) kyllä, useita kertoja
b) kyllä, 1-2 kertaa
c) en ole kaatunut

33. Oletteko kaatunut loukaten itsenne

a) en
b) kyllä, miten loukkaannuitte
_____

Elinoloihinne ja –tapoihinne liittyvät kysymykset:

34. Oletteko vielä työelämässä

a) kyllä b) en. Olen eläkkeellä vuodesta _____

35. Jos olette eläkkeellä, jäittekö **alunperin**

a) vanhuuseläkkeelle
b) varhennetulle vanhuuseläkkeelle tai vastaavalle
c) osa-aikaeläkkeelle
d) työkyvyttömyyseläkkeelle
e) työttömyyseläkkeelle
f) minulla oli henkilökohtainen eläkesopimus

36. Mikä on nykyinen siviilisäätynne?

a) avioliitossa tai avoliitossa
b) leski, _____ vuotta
c) eronnut _____ vuotta
d) naimaton

37. Tupakoitteko nykyisin?

a) en ole koskaan tupakoinut
b) lopetin vuonna _____
c) kyllä tupakoin

38. Montako vuotta olette elämänne aikana tupakoinut?

_____ vuotta

39. Vain **nykyisin** tupakoiville: miten paljon poltatte keskimäärin päivässä?

a) savukkeita _____ kpl / pv
b) piippua _____ piipullista / pv
c) sikareja _____ kpl / pv
d) pikkusikareja _____ kpl / pv
e) nuuskaa, tms. _____ kpl / pv

40. Käytättekö nykyisin alkoholia?

a) en ole koskaan käyttänyt tai käyttänyt hyvin harvoin
b) olen käyttänyt aiemmin, mutta lopettanut vuonna _____
c) kyllä

41. Mikä on ollut keskimäärin alkoholin **viikkokäyttönne** viimeksi kuluneen vuoden aikana?

a) olutta _____ pullollista / viikko (pullo = 1/3 litraa)
b) viiniä _____ lasillista / viikko (lasi = 12 cl)
c) väkeviä juomia _____ grogia (ravintola-annosta vastaava määrä= 4 cl) / viikk

42. Harrastatteko liikuntaa säännöllisesti viikoittain?

a) en b) kyllä _____ tuntia / viikko

43. Kuinka paljon keskimäärin kävelette päivässä

a) en lainkaan
b) vähemmän kuin 1 km
c) 1-3 km
d) yli 3 km

44. Kuinka monta kertaa viikossa harrastatte hengästymistä ja hikoilua aiheuttavaa liikuntaa

_____ kertaa viikossa

45. Mikä on mielestänne nykyinen ruumiillinen kuntonne

a) erinomainen
b) varsin hyvä
c) hyvä
d) tyydyttävä
e) huono

Nykyiseen terveydentilaanne liittyvät kysymykset:

46. Mikäli tiedossa, merkitkää tähän

- nykyinen painonne
- viimeisin verenpainelukemanne _____/_____ mmHg
- viimeisin kolesterolilukemanne (s-kol) _____ mmol/l
- viimeisin verensokerilukemanne (B-gluk) _____

47. Missä sairaaloissa olette ollut hoidossa viimeisen vuoden aikana?

_____

_____

_____

_____

Elämänasenteisiin liittyvät kysymykset:

48. Oletteko tyytyväinen elämäänne?

a) kyllä b) en

49. Onko Teillä tulevaisuudensuunnitelmia?

a) kyllä b) ei

50. Onko Teillä elämänhalua?

a) kyllä b) ei

51. Kärsittekö yksinäisyydestä?

a) harvoin tai ei koskaan
b) toisinaan
c) usein tai aina

52. Miten arvioitte elämänkaartanne kokonaisuutena (elämänkokemuksia, rikkautta, sisältöä). Käyttäkää kouluarvosanoja: 4 = huonoin, 10 = paras

4 5 6 7 8 9 10

53. Kuinka onnelliseksi / onnettomaksi elämässä tunnette itsenne tällä hetkellä? Pyydämme Teitä merkitsemään oheiselle suoralle rastin (X) siihen kohtaan, joka parhaiten kuvaa tilannetta

Hyvin onneton — Hyvin onnellinen

54. Kuinka stressaavana / rasittavana koitte työuranne kokonaisuutena. Merkitkää X kohtaan, joka mielestänne parhaiten kuvaa tilannetta

Hyvin rasittava — Ei lainkaan rasittava

Seuraavaksi esitetään erilaisia väittämiä siitä miltä elämänne tuntuu. Lukekaa ne tarkkaan ja rastittakaa teidän kohdallenne sopivin vaihtoehto.

	harvoin tai ei koskaan	joskus	usein	enimmäkseen tai aina
54. Tunnen itseni alakuloiseksi ja surulliseksi	1	2	3	4
55. Aamuisin tunnen olevani Parhaimmillani	1	2	3	4
56. Saan itkukohtauksia tai minulla on usein tarvetta itkeä	1	2	3	4
57. Öisin nukun huonosti	1	2	3	4
58. Syön yhtä paljon kuin ennenkin	1	2	3	4
59. Nautin edelleen sukupuoli-elämästä	1	2	3	4
60. Huomaan laihtuvani	1	2	3	4
61. Kärsin ummetuksesta	1	2	3	4
62. Sydämeni lyö nopeammin kuin tavallisesti	1	2	3	4

	harvoin tai ei koskaan	joskus	usein	enimmäkseen tai aina
63. Väsyn ilman mitään syytä	1	2	3	4
64. Pystyn ajattelemaan yhtä selkeästi kuin ennenkin	1	2	3	4
65. Asiat sujuvat minulta yhtä				

helposti kuin ennenkin ..... 1 ..... 2 ..... 3 4
66. Olen rauhaton enkä pysy aloillani 1 ..... 2 ..... 3 4
67. Olen toiveikas tulevaisuuden
suhteen ..... 1 ..... 2 ..... 3 4
68. Olen ärtyneempi kuin tavallisesti . 1 ..... 2 ..... 3 4
69. Minun on helppo tehdä ratkaisuja 1 ..... 2 ..... 3 4
70. Tunnen olevani hyödyksi ja
että minua tarvitaan ..... 1 ..... 2 ..... 3 4
71. Elämäni on melko täyteläistä ..... 1 ..... 2 ..... 3 4
72. Minusta tuntuu että olisi muille
parempi, jos olisin kuollut ..... 1 ..... 2 ..... 3 4
73. Nautin edelleen sellaisten asioiden
tekemisestä, joita minulla oli
ennenkin tapana tehdä. ..... 1 ..... 2 ..... 3 4

Mahdollisiin sairauksiin ja lääkkeisiin liittyvät kysymykset:

Onko lääkäri todennut Teillä seuraavia sairauksia:

	EI	**KYLLÄ**	oletteko nykyisin **sen takia** lääkärin-hoidossa?	käytättekö nykyisin **sen takia lääkehoitoa**?
74. muistihäiriöitä	☐	☐	☐	☐
75. aivohalvaus tms.	☐	☐	☐	☐
76. kohonnut verenpaine	☐	☐	☐	☐
77. sepelvaltimotauti	☐	☐	☐	☐
78. sydämen vajaatoiminta	☐	☐	☐	☐
79. sydäninfarkti	☐	☐	☐	☐
80. rintakipua rasituksessa	☐	☐	☐	☐
81. keuhkoastma	☐	☐	☐	☐
82. keuhkolaajentuma tms.	☐	☐	☐	☐
83. alaraajojen verenkiertohäiriö	☐	☐	☐	☐
84. alaraajan valtimotukos	☐	☐	☐	☐
85. alaraajan valtimoahtauma	☐	☐	☐	☐
86. sokeritauti (diabetes)	☐	☐	☐	☐
87. syöpä	☐	☐	☐	☐
88. sappikiviä	☐	☐	☐	☐
89. nivelreuma	☐	☐	☐	☐
90. nivelkuluma (rikko)				
- polvi	☐	☐	☐	☐
- lonkka	☐	☐	☐	☐
- käsi	☐	☐	☐	☐
- muu, mikä _____	☐	☐	☐	☐

	EI	KYLLÄ	oletteko nykyisin **sen takia** lääkärinhoidossa?	käytättekö nykyisin **sen takia** lääkehoitoa?
91. muu nivelsairaus	☐	☐	☐	☐
92. tuki- ja liikuntaelinten sairaus	☐	☐	☐	☐
94. lievä psyykkinen häiriö (esim. lievä masennustila tai neuroosi)	☐	☐	☐	☐
95. vaikea psyykkinen sairaus (esim. vaikea masennustila tai mielisairaus)	☐	☐	☐	☐
96. vatsahaava tai pohjukkaissuolihaava	☐	☐	☐	☐
97. tapaturman aiheuttama pysyvä vamma	☐	☐	☐	☐
98. virtsatietulehdus	☐	☐	☐	☐
99. eturauhasvaiva	☐	☐	☐	☐
100. muu pitkäaikainen sairaus tai vamma, mikä _____	☐	☐	☐	☐

101. Jos Teillä on krooninen sairaus, vika tai vamma, heikentääkö se toimintakykyänne?

a) ei b) kyllä

102. Onko Teille tehty sydämen ohitusleikkaus tai pallolaajennus?

a) ei b) kyllä vuonna_____

103. Kuinka monta **viikkoa** yhteensä olette viimeisen **2 vuoden aikana** ollut sairaalahoidossa

a) en yhtäkään b) _____ viikkoa

104. Käytättekö säännöllisesti jotain lääkettä (**myös käsikauppalääkkeet**, esim. aspiriini, primaspan, disperin)

a) ei b) kyllä

105. Kirjoittakaa tähän **säännöllinen lääkityksenne** (viimeisen 6 kuukauden aikana käytetty), **sekä resepti- että käsikauppalääkkeet, LÄÄKKEEN NIMI JA ANNOS**

_____

_____

_____

_____

_____

_____

_____

_____

_____

Toimintakykyänne mittaavat kysymykset:

106. Onko terveytenne yleisesti ottaen

(ympyröikää yksi vaihtoehto)

a) erinomainen
b) varsin hyvä
c) hyvä
d) tyydyttävä
e) huono

107. Jos vertaatte nykyistä terveydentilaanne vuoden takaiseen, onko terveytenne yleisesti ottaen

(ympyröikää yksi vaihtoehto)

a) tällä hetkellä paljon parempi kuin vuosi sitten
b) tällä hetkellä jonkin verran parempi kuin vuosi sitten
c) suunnilleen samanlainen
d) tällä hetkellä jonkin verran huonompi kuin vuosi sitten
e) tällä hetkellä paljon huonompi kuin vuosi sitten

Seuraavassa luetellaan erilaisia päivittäisiä toimintoja. Rajoittaako terveydentilanne nykyisin suoriutumistanne seuraavista päivittäisistä toiminnoista? Jos rajoittaa, kuinka paljon?

	(ympyröikää yksi numero joka riviltä) kyllä, rajoittaa paljon	kyllä, rajoittaa hiukan	ei rajoita lainkaan
108. huomattavia ponnistuksia vaativat toiminnat (esimerkiksi juokseminen, raskaiden tavaroiden nostelu, rasittava urheilu)	1	2	3
109. kohtuullisia ponnistuksia vaativat toiminnat, kuten pöydän siirtäminen, imurointi, keilailu	1	2	3
110. ruokakassien nostaminen tai kantaminen	1	2	3
111. nouseminen portaita useita kerroksia	1	2	3
112. nouseminen portaita yhden kerroksen	1	2	3
113. vartalon taivuttaminen, polvistuminen, kumartuminen	1	2	3
114. noin kahden kilometrin matkan kävely	1	2	3
115. noin puolen kilometrin matkan kävely	1	2	3
116. noin 100 metrin matkan kävely	1	2	3
117. kylpeminen tai pukeutuminen	1	2	3

Onko Teillä viimeisen 4 viikon aikana ollut **ruumiillisen terveydentilanne takia** alla mainittuja ongelmia tavanomaisissa päivittäisissä tehtävissänne?

	(ympyröikää yksi numero joka riviltä) kyllä	ei
118. Vähensitte työhön tai muihin tehtäviin käyttämäänne aikaa	1	2
119. Saitte aikaiseksi vähemmän kuin halusitte	1	2
120. Terveydentilanne asetti teille rajoituksia joissakin työ- tai muissa tehtävissä	1	2
121. Töistänne tai tehtävistänne suoriutuminen tuotti vaikeuksia (olette joutunut esim. ponnistelemaan tavallista enemmän)	1	2

Onko Teillä viimeisen 4 viikon aikana ollut **tunne-elämään liittyvien** vaikeuksien (esim. masentuneisuus tai ahdistuneisuus) takia alla mainittuja ongelmia työssänne tai muissa tavanomaisissa päivittäisissä tehtävissänne?

	(ympyröikää yksi numero joka riviltä) kyllä	ei
122. Vähensitte työhön tai muihin tehtäviin käyttämäänne aikaa	1	2
123. Saitte aikaiseksi vähemmän kuin halusitte	1	2
124. Ette suorittanut töitänne tai muita tehtäviänne yhtä huolellisesti kuin tavallisesti	1	2

125. **Missä määrin** ruumiillinen terveydentilanne tai tunne-elämän vaikeudet ovat viimeisen 4 viikon aikana häirinneet tavanomaista (sosiaalista) toimintaanne perheen, ystävien, naapureiden tai muiden ihmisten parissa?

(ympyröikää yksi vaihtoehto)

a) ei lainkaan
b) hieman
c) kohtalaisesti
d) melko paljon
e) erittäin paljon

126. Kuinka voimakkaita ruumiillisia kipuja Teillä on ollut viimeisen 4 viikon aikana? (ympyröikää yksi vaihtoehto)

a) ei lainkaan
b) hyvin lieviä
c) lieviä
d) kohtalaisia
e) voimakkaita
f) erittäin voimakkaita

127. Kuinka paljon kipu on häirinnyt tavanomaista toimintaanne (kotona tai kodin ulkopuolella) viimeisen 4 viikon aikana?
(ympyröikää yksi vaihtoehto)

a) ei lainkaan
b) hieman
c) kohtalaisesti
d) melko paljon

e) erittäin paljon

Seuraavat kysymykset koskevat sitä, miltä Teistä on tuntunut viimeisen 4 viikon aikana. Merkitkää kunkin kysymyksen kohdalla se numero, joka parhaiten kuvaa tuntemuksianne.

Kuinka suuren osan ajasta olette viimeisen 4 viikon aikana ... (ympyröikää yksi numero joka riviltä)

	koko ajan	suurimman osan aikaa	huomattavan osan aikaa	jonkin aikaa	vähän aikaa	en lainkaan
128. tuntenut olevanne täynnä elinvoimaa	1	2	3	4	5	6
129. ollut hyvin hermostunut	1	2	3	4	5	6
130. tuntenut mielialanne niin matalaksi, ettei mikään ole voinut teitä piristää	1	2	3	4	5	6
131. tuntenut itsenne tyyneksi ja rauhalliseksi	1	2	3	4	5	6
132. ollut täynnä tarmoa	1	2	3	4	5	6
133. tuntenut itsenne alakuloiseksi ja apeaksi	1	2	3	4	5	6
134. tuntenut itsenne "loppuunkuluneeksi"	1	2	3	4	5	6
135. ollut onnellinen	1	2	3	4	5	6
136. tuntenut itsenne väsyneeksi	1	2	3	4	5	6

137. **Kuinka suuren osan ajasta** ruumiillinen terveydentilanne tai tunne-elämänvaikeudet ovat viimeisen 4 viikon aikana häirinneet tavanomaista sosiaalista toimintaanne (ystävien, sukulaisten, muiden ihmisten tapaaminen)?
(ympyröikää yksi vaihtoehto)

a) koko ajan
b) suurimman osan aikaa
c) jonkin aikaa
d) vähän aikaa
e) ei lainkaan

Kuinka hyvin seuraavat väittämät pitävät paikkansa Teidän kohdallanne?

(ympyröikää yksi numero joka riviltä)

	pitää ehdottomasti paikkansa	pitää enimmäkseen paikkansa	en osaa sanoa	enimmäkseen ei pidä paikkansa	ehdottomasti ei pidä paikkansa
138. Minusta tuntuu, että sairastun jonkin verran helpommin kuin muut ihmiset	1	2	3	4	5
139. Olen vähintään yhtä terve kuin kaikki muutkin tuntemani ihmiset	1	2	3	4	5
140. Uskon, että terveyteni tulee heikkenemään	1	2	3	4	5
141. Terveyteni on erinomainen	1	2	3	4	5

142. Mikäli lähetämme Teille vielä myöhemmin kutsun lisätutkimuksiin, oletteko mahdollisesti niihin halukas osallistumaan Meilahden sairaalassa. Tutkimukset ovat maksuttomia.

a) kyllä b) en

Antamiani tietoja voidaan käyttää saatekirjeessä mainittuihin tutkimustarkoituksiin.

Paikka ja päivämäärä	Allekirjoitus	**Puhelinnumero** johon voimme ottaa tarvittaessa yhteyttä

Tarkistattehan vielä, että olette vastannut kaikkiin kysymyksiin.

PARHAAT KIITOKSEMME VASTAUKSISTANNE

Appendix III. Mini-Nutritional Assessment (MNA, in Finnish) (Guigoz et al. 2002, Guigoz 2006).

RAVITSEMUSTILAN ARVIOINTI - MINI-NUTRITIONAL ASSESSMENT

Ravitsemustilan arviointi MNA

Nimi_____ Sukupuoli_____ Ikä_____

Pituus (cm)_____ Paino (kg)_____ Päivämäärä_____

Merkitse pisteet ruutuihin ja laske yhteen.

Jos seulonnan kokonaispistemäärä on 11 tai vähemmän, jatka loppuun asti

I SEULONTA

1. Onko ravinnonsaanti vähentynyt viimeisen kolmen kuukauden aikana ruokahaluttomuuden, ruuansulatusongelmien, puremis- tai nielemisvaikeuksien takia
- 0 = erittäin huono ruokahalu
- 1 = kohtalainen ruokahalu
- 2 = Hyvä ruokahalu, ei ruokahaluttomuutta

2. Painonpudotus kolmen viime kuukauden aikana
- 0 = painonpudotus yli 3 kg
- 1 = ei tiedä
- 2 = painonpudotus 1-3 kg
- 3 = ei painonpudotusta

3. Liikkuminen
- 0 = vuode- tai pyörätuolipotilas, ei käy ulkona
- 1 = pääsee ylös sängystä, mutta ei käy ulkona
- 2 = liikkuu ulkona (myös pyörätuolissa oleva)

4. Onko viimeisen kolmen kuukauden aikana ollut psyykkistä stressiä tai akuutti sairaus
- 0 = kyllä
- 2 = ei

5. Neuropsykologiset ongelmat
- 0 = dementia tai depressio
- 1 = lievä dementia tai depressio
- 2 = ei psykologisia ongelmia

6. Painoindeksi eli BMI (= paino / pituus *; kg/m²)
- 0 = BMI <19
- 1 = 19 ≤ BMI < 21
- 2 = 21 ≤ BMI < 23
- 3 = BMI ≥ 23

Seulontapisteet (maks. 14)

≥ 12 pistettä Normaali - eri riskiä - ei tarvetta jatkaa testiä

< 12 pistettä Aliravitsemus mahdollinen – jatka testiä

II ARVIOINTI

7. Asuuko haastateltava kotona
- 0 = ei
- 1 = kyllä

8. Onko päivittäisessä käytössä useampi kuin kolme reseptilääke
- 0 = kyllä
- 1 = ei

9. Painehaavaumia tai muita haavoja iholla
- 0 = kyllä
- 1 = ei

10. Päivittäiset lämpimät ateriat (sisältää puurot ja vellit)
- 0 = 1 ateria
- 1 = 2 ateriaa
- 2 = 3 ateriaa

10. Sisältääkö ruokavalio vähintään
- yhden annoksen maitovalmisteita (maito, juusto, piimä, viili) päivässä — kyllä / ei
- kaksi annosta tai enemmän kananmunia viikossa (myös ruuissa, esim. laatikot) — kyllä / ei
- lihaa, kalaa tai kanaa joka päivä — kyllä / ei

0 = jos 0 tai 1 kyllä-vastausta
0,5 = jos 2 kyllä-vastausta
1 = jos 3 kyllä-vastausta

12. Kuuluuko päivittäiseen ruokavalioon kaksi tai useampia annoksia hedelmiä tai kasviksia
- 0 = ei
- 1 = kyllä

13. Päivittäinen nesteen juonti (esim. kahvi, tee, maito, mehu, kotikalja tai vesi)
- 0 = alle 3 lasillista
- 0,5 = 3 - 5 lasillista
- 1 = enemmän kuin 5 lasillista

14. Ruokailu
- 0 = syötettävä / tarvitsee ainakin osittain apua
- 1 = syö itse, mutta hankalaa
- 2 = syö itse ongelmitta

15. Oma näkemys ravitsemustilasta
- 0 = kokee syövänsä liian vähän / liian yksipuolisesti
- 1 = ei osaa sanoa / pieniä ongelmia
- 2 = kokee syövänsä riittävästi ja monipuolisesti

16. Oma näkemys terveydentilasta verrattuna muihin samanikäisiin
- 0 = huonompi
- 0,5 = ei tiedä
- 1 = yhtä hyvä
- 2 = parempi

17. Olkavarren keskikohdan ympärysmitta (OVY cm)
- 0 = OVY < 21 cm
- 0,5 = OVY 21-22 cm
- 1,0 = OVY > 22 cm

18. Säären ympärysmitta (SYM cm)
- 0 = SYM < 31 cm
- 1 = SYM ≥ 31 cm tai enemmän

Pisteet yhteensä II Arviossa (max. 16) _____

Pisteet yhteensä I Seulonnassa (max 14) _____

Yhteispisteet (max. 30) _____

ASTEIKKO:
> 23.5 pistettä = hyvin ravittu
17 - 23.5 pistettä = aliravitsemusriski
< 17 pistettä = aliravittu

Finravinto –tutkimusryhmä. 1998. The 1997 Dietary Survey of Finnish Adults. Publications of the National Public Health Institute B8/1998. Helsinki.

Guigoz Y, Vellas B & Garry P. 1996. Assessing the Nutritional Status of the Elderly: the Mini Nutritional Assessment as Part of the Geriatric Evaluation. Nutrition Reviews 4 (9), 559-565.

Ravitsemusarvio ("Mini Nutritional Assessment"). 1997. Retrieved 11.4.1998, from http://www.gernet.fi.

Soini H. 2004. Nutrition in Patients Receiving Home Care. Annales Universitatis Turkuensis D 638. Turun yliopisto, Turku.

Iäkkään henkilön ravitsemustilan arviointiin ja seurantaan suunnitellun MNA (Mini Nutritional Assessment) -mittarin avulla on mahdollista tunnistaa ne iäkkäät ihmiset, joiden virhe- tai aliravitsemuksen ja sen vahingollisten seurauksien riski on kasvanut. Tämä auttaa ennaltaehkäisevien toimenpiteiden kohdistamisessa ja aloittamisessa. MNA -testin tuloksen perusteella ei kuitenkaan voida tehdä päätelmiä esimerkiksi proteiini-aliravitsemuksesta ja sen riskistä. Niiden selvittämiseksi tarvitaan laboratoriokokeita. MNA -testi voidaan suorittaa säännöllisesti avohoidossa tai laitoshoidossa.

MNA koostuu seulonta- ja arviointiosuudesta ja se voidaan suorittaa alle 15 minuutissa. Jos tutkittava henkilö saa seulonnassa korkean pistemäärän (12 pistettä tai enemmän), ei arviointia tarvitse jatkaa. Muussa tapauksessa vastataan kaikkiin kysymyksiin.

Huomioita mittaamiseen

6. Pituus

Pituus mitataan ilman jalkineita, seisten mahdollisimman suorana selkä seinää vasten ja kantapäät maassa. Mikäli pituutta ei voida mitata, voidaan käyttää tietoa lähiaikoina mitatusta pituudesta tai potilaan ilmoittamaa pituutta (mikäli luotettava ja realistinen). Mikäli nämäkään eivät ole mahdollisia voidaan käyttää esimerkiksi kyynärvarren pituuden tai polven korkeuden mittaa apuna pituuden arvioinnissa. Lisätietoja vaihtoehtoisista mittauksista löytyy aiheeseen liittyvästä kirjallisuudesta tai nettisivuilta.

17. Olkavarren ympärysmitta

Mittausta varten tarvitaan mittanauha ja kynä, jolla voi tehdä merkinnän ihoon. Mittaus tehdään siitä kädestä, joka ei ole dominoiva (eli oikeakätisellä vasemmasta kädestä). Olkavarren keskikohta mitataan koukistetusta kädestä ja merkitään kynällä. Keskikohdasta mitataan ympärysmitta, kun käsi roikkuu vapaasti sivulla.

18. Säären ympärysmitta

Ikäihminen voi istua tai seistä siten, että paino on molemmilla jaloilla. Säären ympärys mitataan säären paksuimmasta kohdalta paljaana olevasta jalasta. Mittaus voidaan tehdä vielä hieman ylemmästä ja alemmasta kohdasta, jotta voidaan varmistua, että mittaustulos on säären paksuimmasta kohdasta.

Appendix IV. Short Physical Performance Battery (SPPB, in Finnish) (Guralnik et al. 1994).

LYHYT FYYSISEN SUORITUSKYVYN TESTISTÖ
Short Physical Performance Battery (SPPB)

TESTIKAAVIO JA SUORITUSTEN PISTEYTYS

Testattavan nimi _____

Päivämäärä _____ _____ 20_____ klo _____

Testaajan nimi _____

Suoritusajat kirjataan kahden desimaalin tarkkuudella (0.00 sekuntia).

1. TASAPAINO

a. Jalat rinnakkain	sekuntia
b. Puolitandem	sekuntia
c. Tandem	sekuntia

Pisteet: _____

2. KÄVELYNOPEUS (4 metriä) omalla kävelyvauhdilla

a. Suoritus ilman apuvälinettä	
b. Suoritus tehtiin apuvälineen kanssa, mikä apuväline?	
1. suoritus	sekuntia
2. suoritus	sekuntia

Pisteet: _____

3. TUOLILTA YLÖSNOUSU (viisi kertaa)

aika _____ sekuntia

Jos testattava ei pysty tekemään testiä kädet ristissä rinnalla (tulos= 0 p.), tehdään testi niin, että tutkittava pitää

a. Kädet vartalon vierellä	toistojen lkm	aika	sekuntia
b. Ottaa kevyesti tukea reisistä	toistojen lkm	aika	sekuntia
c. Ottaa voimakkaasti tukea reisistä	toistojen lkm	aika	sekuntia

Pisteet: _____

Laske yhteen pisteet testeistä 1, 2 ja 3 = /12

Huomioita: _____

_____

1. TASAPAINO

Jalat rinnakkain -seisonta

Jalkaterät ovat rinnakkain ja kiinni toisissaan 10 sekuntia.

< 10 s (0 p.) → Siirry kävelytestiin

10 s (1 p.)

Puolitandem-seisonta

Takimmaisen jalan isonvarpaan tyvinivel etummaisen jalan kantapään sisäosaa vasten 10 sekuntia.

< 10 s (+0 p.) → Siirry kävelytestiin

10 s (+ 1 p.)

Tandem-seisonta

Toisen jalan kantapää toisen jalan edessä, kantapää ja varpaat kiinni toisissaan.

10 s (+ 2 p.)
3–9.99 s (+ 1 p.)
3 s (+ 0 p.)

2. KÄVELYNOPEUS

Tavanomainen kävelynopeus

4 metrin matkalta.
2 suoritusta, joista paras valitaan tulokseksi.

< 4.82 s	4 p.
4.82–6.20 s	3 p.
6.21–8.70 s	2 p.
> 8.7 s	1 p.
Ei pysty tekemään	0 p.

3. YLÖSNOUSU TUOLISTA

Testaus

Testattava kokeilee nousta yhden kerran tuolista käsivarret koukistettuna rinnan päälle.

Ei onnistu
Testitulos (0 p.)

Toistettu ylösnousu (5x)

Toistetaan, käsivarret rinnan päälle koukistettuna, ylösnousu tuolista viisi kertaa niin nopeasti kuin mahdollista.

< 11.19 s	4 p.
11.20–13.69 s	3 p.
13.70–16.69 s	2 p.
>16.7 s	1 p.
> 60 s tai ei pysty tekemään	0 p.

Appendix V. Mini-Mental State Examination (MMSE, in Finnish) (Folstein et al. 1975).

MINI-MENTAL STATE EXAMINATION

POTILAS: _____ SYNTYMÄAIKA:_____

TUTKIJA: _____ PVM:_____

Seuraavassa esitän Teille erilaisia pieniä muistiin ja älyllisiin toimintoihin liittyviä kysymyksiä ja tehtäviä:

		Väärin	Oikein
1.	**Mikä vuosi nyt on?**	0	1
2.	**Mikä vuodenaika nyt on?** (talvi = joulu, tammi, helmi kevät = maalis, huhti, touko kesä = kesä, heinä, elo syksy = syys, loka, marras; aina ± 1 vko)	0	1
3.	**Monesko päivä tänään on? (± 1 pv)**	0	1
4.	**Mikä viikonpäivä tänään on?**	0	1
5.	**Mikä kuukausi nyt on?**	0	1
6.	**Missä maassa olemme?**	0	1
7.	**Missä maakunnassa olemme?** (Myös vanhan lääninjaon mukaiset vastaukset hyväksytään)	0	1
8.	**Mikä on tämän paikkakunnan nimi?**	0	1
9.	**Mikä on tämä paikka jossa olemme?** (Sairaalan/terveyskeskuksen nimi, kotiosoite)	0	1
10.	**Monennessako kerroksessa olemme?**	0	1
11.	**Seuraavassa pyydän Teitä painamaan mieleen kolme sanaa. Kun olen sanonut ne, toistakaa perässäni.** (Kaksi vaihtoehtoista sarjaa) **PAITA – RUSKEA – VILKAS** **RUUSU – PALLO – AVAIN** PAITA RUUSU 0 1 RUSKEA tai PALLO 0 1 VILKAS AVAIN 0 1 (Merkitään ensimmäisellä kerralla muistetut sanat. Jos ensimmäisessä toistossa tulee virheitä, sanoja kerrataan, kunnes kaikki kolme sanaa on opittu.) Toistoja____(enintään 5 kertaa).		
12.	**Nyt pyydän Teitä vähentämään 100:sta 7 ja saamastanne jäännöksestä 7 ja edelleen vähentämään 7, kunnes pyydän lopettamaan.** 93..... 0 1 86..... 0 1 79..... 0 1 72..... 0 1 65..... 0 1 (Kysymys voidaan toistaa kerran, jos sitä ei heti ymmärretä. Jos henkilö tekee välillä virheen, mutta jatkaa siitä oikein vähentäen 7 virheellisestä luvusta, tulee vääriä vastauksia 1. Kynää ja paperia ei saa käyttää.)		

		Väärin	Oikein
13.	**Mitkä olivat ne kolme sanaa, jotka pyysin Teitä painamaan mieleenne?** (Sanojen järjestyksellä ei ole merkitystä.) PAITA RUUSU 0 1 RUSKEA tai PALLO 0 1 VILKAS AVAIN 0 1		
14.	**Nyt kysyn Teiltä kahden esineen nimeä.** **a) Mikä tämä on?** – näytetään rannekelloa 0 1 **b) Mikä tämä on?** – näytetään lyijykynää 0 1		
15.	**Nyt luen Teille lauseen. Pyydän Teitä toistamaan sen perässäni:** **EI MITÄÄN MUTTIA EIKÄ JOSSITTELUA** 0 1 (Annetaan piste vain, jos lause on täysin oikein. Lausetta ei saa toistaa.)		
16.	**Seuraavaksi annan Teille paperin ja pyydän Teitä tekemään sille jotain.** (Paperi asetetaan pöydälle tutkittavan eteen.) **Ottakaa paperi vasempaan käteenne. Taittakaa se keskeltä kahtia ja asettakaa polvienne päälle.** (Ohjeita ja lausetta ei saa toistaa eikä henkilöä saa auttaa.) Ottaa paperin vasempaan käteen 0 1 Taittaa sen 0 1 Asettaa paperin polville 0 1		
17.	**Näytän Teille tekstin "SULKEKAA SILMÄNNE". Pyydän Teitä lukemaan sen ääneen ja noudattamaan sen ohjetta.** 0 1 (Annetaan piste vain, jos sekä lukee tekstin että sulkee silmänsä.)		
18.	**Kirjoittakaa kokonainen lyhyt lause mielenne mukaan.** (ks. seuraava sivu) 0 1 (Yksi piste, jos lause on ymmärrettävä ja siinä on ainakin subjekti ja predikaatti. Kirjoitusvirheet eivät vaikuta.)		
19.	**Voisitteko piirtää tämän kuvion alapuolelle samanlaisen kuvion.** (ks. seuraava sivu) 0 1 (Annetaan piste, jos kaikki sivut ja kulmat ovat tallella ja leikkauspinta on nelikulmainen.)		

MMSE-testin pistemäärä _____ /30

KÄÄNNÄ

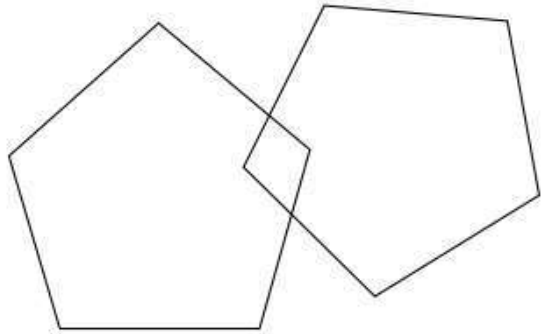
Kirjoittaisitteko lauseen tähän.

_____

_____

_____

Piirtäisittekö tämän kuvion alapuolelle samanlaisen kuvion.



SULKEKAA SILMÄNNE